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OF THE NEW YORK ACADEMY OF MEDICINE

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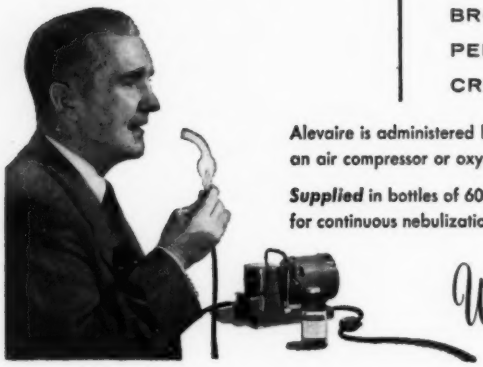

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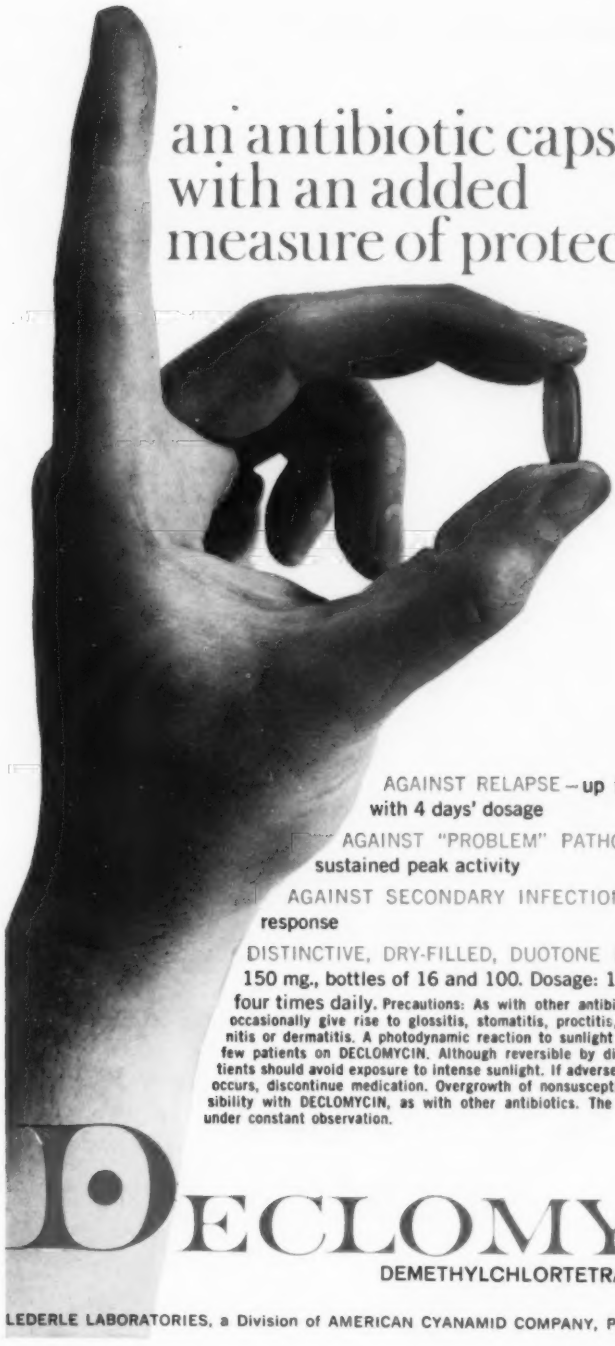

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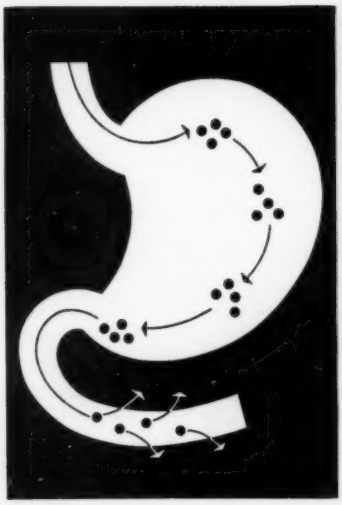

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1. Griffith, R. S.: Antibiotic Med. & Clin. Therapy, 7:320, 1960.

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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NEUROLOGICAL ASPECTS OF INTERNAL CAROTID OBSTRUCTION*

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IN order to understand the clinical signs and symptoms which may develop when the internal carotid artery is occluded, it is important to review briefly the anatomy of this vessel, particularly with reference to its anastomotic connections.

The internal carotid artery is a primary branch of the common carotid artery. It supplies the anterior two thirds of the cerebral hemisphere and a major portion of the basal nuclei through the middle and anterior cerebral arteries. After it enters the cranial cavity, the internal carotid continues as the middle cerebral artery after giving off a minor branch to the orbit, the ophthalmic artery, and a major branch to the anterior portion of the cerebral hemisphere, the anterior cerebral artery.

The internal carotid artery and its branches have three anastomotic systems:

1. The largest and most important of these is through the vessels forming the circle of Willis. The internal carotid systems on the right and left side are united by the anterior communicating artery, an un-

* Presented at the Fourth Annual Postgraduate Week, *Frontiers in Medicine and Surgery*, of The New York Academy of Medicine, October 28, 1960.

paired connection between the two anterior cerebral arteries. The internal carotid arteries are connected with the posterior cerebral arteries of the vertebral-basilar systems by the paired posterior communicating arteries.

2. The second set of anastomoses is by way of meningeal arteries on the surface of the cerebral hemispheres. Branches of the middle cerebral unite with vessels from the posterior and anterior cerebral arteries, and the anterior cerebral with branches of the middle and posterior cerebral arteries. Thus there are connections between the two major branches of the internal carotid and also between these vessels and the branches of the posterior cerebral of the vertebral-basilar system.

In addition, there are also direct connections between the superficial cerebral branches of the three major cerebral arteries with their fellow vessels of the opposite hemisphere.

3. The ophthalmic branch of the internal carotid makes connection with the homolateral external carotid artery by way of branches from the external and internal maxillary artery of the latter.

All of the above anastomoses have been demonstrated anatomically[1] and by angiography.[2, 3] It is important to keep these connections in mind in analyzing the clinical effects of carotid occlusion.

Historical Considerations

The first description of occlusion of the internal carotid artery is credited to Willis, in 1664. Chiari,[4] in 1905, stressed the importance of the extracranial part of the carotid arteries and the frequency of arteriosclerotic changes at the carotid bifurcation. In spite of this work of Chiari's, very little attention was paid to the extracranial vessels in patients with cerebral vascular accidents until the introduction of cerebral angiography by Moniz,[5] in 1927. Since then, numerous cases have been reported by Fisher,[6, 7] Johnson and Walker,[8] Paillas and Bonnal,[9] Gurdjian and Webster,[10] and Riishede.[11]

Frequency of Internal Carotid Thrombosis

It is difficult to determine the frequency of internal carotid thrombosis as the cause of cerebral apoplexy. This is due to the rarity with which the vessels in the neck are studied at necropsy and the slowness of clinicians to adopt routine angiography in the study of patients with cerebral vascular lesions, because of the fear of complications.

In 14 of the 94 cases with cerebral vascular lesions studied angiographically by Riishede,[11] the carotid artery was the site of the thrombosis (internal carotid 13, external carotid 1). There seems to be definite predilection for the lesion to involve the left side, presumably related to the fact that the left common carotid artery arises directly from the arch of the aorta. The extracranial portion of the internal carotid, usually near its point of origin, is commonly the site of the lesion. Males are more frequently affected than females.

Symptomatology

In the absence of any functional anastomoses, thrombosis of the internal carotid neck should result in ischemia of the eye and complete necrosis of the anterior two thirds of the cerebral hemisphere, with resulting homolateral amblyopia, contralateral hemiplegia, hemianesthesia and hemianopia. Aphasia will also be present when the major hemisphere is involved. In the majority of the cases, the lesion is much less extensive. The anterior portion of the frontal lobe is usually preserved because of the adequacy of circulation through the anterior communicating artery, and the posterior portion of the parietal lobe may be spared because of the superficial meningeal anastomoses. Other factors which influence the extent of the lesion are the adequacy of the connections between the ophthalmic artery and branches of the external carotid artery; and the presence of arteriosclerosis in other cerebral vessels. In fact, it is not rare for the internal carotid to be completely thrombosed without any clinical evidence of this lesion. This is particularly true if the thrombosis is of slow evolution. In such cases, symptoms may develop when the collateral circulation for some reason becomes inadequate[12] (fall in systemic blood pressure, development of arteriosclerotic changes in the anastomoses vessels, etc.). The symptoms in these cases may be transient and are described by the term: "acute carotid insufficiency"—or they may be permanent.

Diagnosis

The diagnosis of carotid thrombosis can be made with certainty only by angiography. The results of this test are not always conclusive, because the internal carotid may fail to fill even though there is no lesion in the vessel.

The diagnosis[13] can be suspected when there are repeated episodes

of transient symptoms, such as unilateral amblyopia, syncope, hemiparesis, or unilateral sensory defects. Differentiation from thrombosis of the middle cerebral artery cannot be made from the neurological signs when there is a sudden onset of hemiplegia, or focal neurological signs referable to dysfunction in the territory of the middle cerebral artery.

Other aids in diagnosis include auscultation of the neck, palpation of the carotid artery in the neck and in the pharynx,[14] ophthalmodynamometry and electroencephalography. No one of these tests is conclusive.

With thrombosis of the internal carotid, there may be an enlargement of the external carotid, and a loud systolic bruit may be heard on auscultation over the vessel. Occasionally it may be possible to determine by palpation that pulsations are absent in the internal carotid artery. Transmission of pulsation from the enlarged external carotid often interferes with this test.

Measurement of the arterial pressure in the eyes may give evidence of a decrease in the pressure on the side of the thrombosis. Adequacy of collaterals from the external carotid to the ophthalmic artery may, however, make the pressure equal in the two eyes.

Electroencephalography[15] may show an accentuation of abnormalities in the damaged hemisphere with changes in the posture of the patient on a tilting table.

Compression of the contralateral carotid artery[16] may result in syncope or a transient hemiplegia when the opposite internal carotid is thrombosed. Syncope may also occur when the lesion is confined to the anterior cerebral artery. The obvious risks of this test have limited its use.

Treatment

The treatment of patients with enduring symptoms of thrombosis of the internal carotid artery is essentially that of any patient with a permanent neurologic defect. In patients with transient symptoms related to recurring insufficiency of the carotid circulation, treatment should be with anticoagulants. It is not indicated when the symptoms and signs are fixed and permanent. Surgical therapy will be discussed by Dr. DeBakey.* Decision regarding the value of surgical therapy

* "Surgical Aspects of Internal Carotid Obstruction", Michael E. DeBakey.

depends upon such factors as the site of the lesion as demonstrated by angiography, and the nature of the symptoms. It is hardly necessary to state that reconstruction of a thrombosed artery cannot be expected to effect any improvement in a patient with hemiplegia or other serious focal neurological signs which have been present for more than a few hours.

There has been insufficient experience with the direct injection into the proximal portion of the artery of substances which have a lytic action on the clot.

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ASPECTS OF CITRIC ACID CHEMISTRY RELATED TO BONE*

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CITRIC acid has been known as an important metabolite of plants and animals for many years. The key and catalytic reactions of citrate were established by Krebs,[1] who demonstrated the function of citrate in the carbohydrate economy of many cells and tissues.

In addition to this general role of citrate in the life of cells, it has become apparent that special localizations of citrate occur in nature, and that this chemical specialization is only indirectly related to the functioning of the tricarboxylic acid cycle.

Evidence for a special role of citrate is to be found in examining the large accumulation of citrate in such varying tissues and fluids as the modified hair cells of citrus fruits,[2] the culture media of *Aspergillus*,[3] bone,[4] seminal fluid[5] and, on occasion, blood and urine.

The special distribution and role of citrate as described above is seen to be mainly extracellular in nature, for even in the case of citrus fruits, the citrate occurs in vacuoles apart from the cytoplasm.

The special function of citrate in bone development and metabolism will be discussed from the standpoint of the chemical reactions of citrate with calcium and phosphate, the effects of the vitamins and hormones on citrate distribution and transport, and finally, the source and synthesis of bone citrate.

* Presented, in part, at the meeting of the Section on Orthopedic Surgery, The New York Academy of Medicine, January 11, 1960.

Citric Acid Chemistry – Relation to Calcium

In turning to the chemical properties of citric acid which may be of importance in biological relationships, one must note the types of compounds which citric acid forms with various cations. With the monovalent cations, citrate simply forms the mono-, di-, and tricarboxylate salts. With divalent ions such as calcium, citrate is capable of forming a variety of compounds depending on the pH and the relative concentrations of both citrate and calcium.

A great deal of importance has been attached to those compounds between citrate and calcium in which the calcium no longer behaves as a cation. It has been demonstrated that such calcium no longer acts to conduct an electric current and does not orient itself to the cathode in conductrometric titrations. Further, such calcium no longer is easily precipitated from solution by the usual precipitating agents such as oxalate or phosphate.

This type of compound between citrate and calcium is called a chelate. The citrate is known variously as the chelating agent, ligand, or sequestrant. The calcium has been chelated, sequestered, complexed, or deionized. In this process not only has calcium become deionized, but the citrate has also become partially deionized. Chelates of many types are known; some are positively charged, some are anions, and others are neutral. In dealing with a chelate, one is dealing with a compound in which one atom or group is bound with a definite force to two or more groups in the same molecule. The fact that one atom is bound to two separate groups in the same molecule means that a ring structure is formed.

In the case of calcium and citrate two chelates are known. One chelate is a five-membered ring involving calcium, a carboxyl group and an hydroxyl group. This is considered to be the most stable form. Another form, a six-membered ring involving a carboxyl (beta to the hydroxyl) and the only hydroxyl group, is known. In solution both forms are in equilibrium. Most of the chelate is present in the five-membered ring, not only because this is the most stable configuration, but because it involves the most acidic carboxyl (alpha to the hydroxyl). Significant amounts of the six-membered ring are, however, present. Examination of the structure indicates two possible identical structures which can give a six-membered ring.

In systems where an excess of citrate is involved, an additional form of calcium citrate is known. In this form the calcium reacts with two moles of citrate. This compound is not a chelate. Calcium citrate in this form is a linear polymer, citrate–calcium–citrate being the repeating units. The polymer is of short life in solution and reverts mainly to the five-membered ring chelate. Its main significance in biological terms is that the salt is a macromolecule and could conceivably give rise to a macromolecule of similar structure but different composition by stepwise replacement of the citrate by another polyvalent anion such as phosphate. This would be analogous to the natural petrification of wood. The possibility that linear calcium citrate may be the template for calcium phosphate in ossification is worthy of further study.

In the foregoing discussion it was pointed out that the citric acid has a great affinity for calcium. Citrate also binds other divalent ions, some of which are also of physiologic importance. Chief among these is magnesium.

Citrate in Relation to Phosphate

In examining the basic chemistry of citrate with special regard to reactions with calcium, a major component of bone, reference was made to another major component of bone, phosphate. Extracellular bone citrate must be considered from the standpoint of reaction with calcium phosphate, as this is the substratum for citrate.

A reaction known as reversion is of considerable biological importance. The acidic salts of calcium phosphate, i.e., mono- and dicalcium phosphate, are both quite soluble. If solutions of these salts or mixtures of these salts are permitted to equilibrate at room temperature, a precipitate forms and the solution becomes considerably more acidic. In this reaction it has been found that the insoluble product formed is tricalcium phosphate. The acidic substance formed is phosphoric acid. It has long been known that sulfuric acid and phosphoric acids would inhibit this process. Several years ago one of us found that citrate, sodium polyphosphates, including adenosine triphosphate, and disodium ethylenediamine tetracetic acid would inhibit this reversion. Traces of chelating agents permit the existence of what appear to be supersaturated solutions of calcium phosphate. Such a property of citrate would make it useful in transport of calcium and phosphate for the remodeling of bone.

From the findings related to citrate inhibition of reversion of calcium phosphate, one would anticipate the solution of insoluble tricalcium phosphate by solutions of citrate. This is, of course, the main interaction between tricalcium phosphate and citrate, and will be discussed further.

At low citrate concentrations, another reaction occurs. Kuyper[6, 7] found that the addition of citrate in extremely low concentrations to saturated tricalcium phosphate solutions resulted in the precipitation of the citrate. We have studied this reaction by adding citrate as well as polyphosphate sequestrants to equilibrated, saturated suspensions of steamed bone meal. At low concentrations of citrate or polyphosphate, not only was the sequestrant precipitated, but it carried with it calcium and phosphate. The coprecipitation has not been explained fully, but is thought to result from the reaction of the hydroxyl group of citrate with the phosphate. This complex ion would then form an insoluble calcium salt. This salt is not completely soluble in more concentrated solutions of citrate.

The phenomenon of coprecipitation of calcium by complexes of phosphate containing other ions such as hydroxyl and fluoride is, of course, well known. The finding that calcium-solubilizing agents also produced precipitation of calcium under these conditions was unexpected. Calcium may be regarded as stabilizing the complex anions of phosphate. Such a property of citrate, i.e., the stabilization of tricalcium phosphate, could be expected to protect bone tricalcium phosphate from solution due to incidental metabolic changes which liberate small amounts of organic acids, including citric acid.

Higher concentrations of citrate have the ability of bringing into solution most forms of calcium phosphate. Calcium fluorophosphates are not solubilized and hydroxyapatite is only partially dissolved by this treatment. More powerful sequestrants are capable of dissolving all of these salts.

In each of the reactions involving calcium phosphate and citrate, it should be noted that the fate of both calcium and phosphate is that they are linked to each other. In those reactions where calcium is solubilized the phosphate is solubilized. Where calcium is precipitated, phosphate is also precipitated. This need not be true where other types of precipitation are involved, but it is true where coprecipitation of the complexing ion occurs.

The chemistry of rock phosphate illustrates some important aspects

of calcium phosphate relations. Rock phosphate is essentially a deposit of marine fossils. It contains on the average 20 per cent phosphoric anhydrides and 3 per cent fluoride. This phosphate and the calcium associated with it are desirable fertilizer materials. However, it is known that such pulverized rock is rather inert when applied to the soil. Except in very acid soils, plants are not able to abstract the calcium and phosphate from the pulverized rock. If the rock is treated with acids such as nitric, sulfuric, or hydrochloric, both the calcium and phosphate of such a preparation are available for plant growth. It has been determined that heating the pulverized rock at temperatures which vaporize hydrogen fluoride will markedly improve the solubility of the resultant phosphate. If unheated rock phosphate is treated with 2 per cent citrate solution, only a small portion of the calcium and phosphate dissolves. If the heated rock is treated with citrate, almost all of the phosphate and calcium dissolves. The solubility of a calcium phosphate specimen in 2 per cent citrate is recognized by the United States Department of Agriculture as a measure of the biological availability of both the calcium and phosphate for both plant and animal nutrition. If citrate has a role in either mobilizing or depositing calcium, it should be clear that the effects on both calcium and phosphate must both be in the same direction. Either both are solubilized or both are precipitated.

Vitamin D and Citrate

It has been demonstrated that both bone and serum citrate are depressed in rickets associated with vitamin D deficiency.[4] Bone citrate slowly returns to normal values with vitamin D therapy. The growing centers return to normal citrate values rather rapidly. The effect of vitamin D on calcium balance and deposition may be interpreted as being secondary to the effect that vitamin D has on citrate distribution. The administration of vitamin D leads first to an elevation of plasma citrate. How this increased citrate enhances calcium uptake from the intestines is not clear. One would anticipate that the formation of the calcium citrate chelate would increase the mobility of the calcium and favor its absorption even under conditions of excess phosphate and hydroxyl ion concentration.

The other major effects of vitamin D leading to calcification (even in the presence of low serum calcium values) and enhanced phosphorus excretion may be explained on the basis of coprecipitation of the calcium

phosphate-citrate complex in bone. The coprecipitated product is of lower phosphorus content and thus would make available to the serum increased phosphate. Such phosphate would be excreted, or at least its resorption by the kidney tubule would be inhibited.

Such an explanation has the advantage of being consistent with the fact that calcification can occur in vitamin D deficient rickets when citrate is administered. Such calcification occurs even in the face of low serum calcium and phosphorus.

The effect of citrate in animals made rachitic by the use of a diet high in calcium and low in phosphorus has been demonstrated by Hamilton and Dewar,[8] and by Shohl.[9] They found that the oral administration of citric acid or sodium citrate could alleviate the symptoms of rickets and could clearly elevate the serum phosphorus. Other workers have used a citric acid-sodium citrate mixture towards the same end, not only in low phosphorus rickets but in the treatment of human osteomalacia.[10] Under these conditions, calcium citrate is not useful, while citric acid or sodium citrate are effective. There have been several attempts to explain the increased calcium and phosphorus uptake following citrate administration on the basis of pH. This seems unlikely, since citric acid administration leads to a slight increase in the acidity of both the gut and the plasma. The use of the sodium salt causes a slight alkalosis. It is true that a decrease in pH would favor the solubility of calcium phosphate in the gut. However, one cannot explain the effect of sodium citrate on this basis.

A more plausible explanation is offered as follows. The rickets produced by the high calcium diet is essentially a low phosphorus rickets. The absolute amount of phosphorus in such a diet is generally sufficient for normal growth. However, its uptake is inhibited by the presence of excess calcium. Any agent which can compete with phosphate for the excess calcium will render the phosphate soluble and available for uptake. It is clear that either citric acid or sodium citrate can perform in this fashion. Calcium citrate administration fails because such citrate can not remove additional calcium and therefore can not liberate phosphate.

Hormones and Citrate

Shorr[11] and his co-workers have demonstrated a cyclic excretion pattern of citric acid in women. The peak excretion of citrate occurs at ovulation. Shorr has shown that the administration of estrogens causes

an excretion of citrate, but that such an effect also requires the presence of progesterone.

Androgens have been shown to inhibit the excretion of citrate. Androgens favor the accumulation of citrate in seminal fluid.

The Hennemans[12] have shown the effects of human growth hormone on citrate distribution. Their data are in agreement with earlier work obtained in studies on animals and acromegalics. The administration of growth hormone leads to a rise in urinary citrate. Calcium is excreted along with the citrate, whereas phosphate is strongly retained. Calcium balance is not negative despite the increased urinary output of calcium. When growth hormone is withdrawn, a marked positive calcium balance occurs.

The effect of parathyroid hormone on bone citrate is not clear. Dickens[4] has shown that animals treated with parathyroid hormone respond by increases in bone citrate. He claimed that minced bones of such treated animals had increased powers of citric acid synthesis. Perkins and Dixon[13] were not able to depress bone citrate levels by parathyroidectomy. The administration of parathyroid hormone to such animals did not cause elevations of bone citrate.

The effect of parathyroid hormone administration on blood and urinary citrate is dramatic and clear. Parathyroid hormone causes an elevation of plasma citrate and calcium.[11] This is followed by increased amounts of these materials in the urine.

The inter-relation between hormones and citric acid distribution raises many questions. Further experimental work is required to explain the significance of shifts in citrate concentration.

Some workers have felt that the changes in citrate induced by growth hormone result from the effect of that hormone on carbohydrate metabolism of soft tissues. It is difficult to accept the concept that circulating citrate represents a significant portion of the carbohydrate pool in the same manner as does glucose. If this were true, one would expect acromegalics to excrete a major portion of their carbohydrates as citrate in the same way that diabetics may lose one hundred grams of glucose daily. The relative impermeability of most cells to citrate argues against the role of circulating citrate as being part of the carbohydrate pool. Circulating citrate is more likely to be a secretory material of soft tissues and bone.

It is not known if the increased amounts of citrate present in blood

under the influence of estrogens, growth, and parathyroid hormones represent increased synthesis by the body under the hormonal influence, or if they represent a depletion of stores from bone. The source of the increased circulating citrate as a response to vitamin D is also not known. It may well be that vitamin D induces citrate to leave parenchymal cells and enter extracellular spaces where it affects calcium and phosphorus uptake. Thus vitamin D would positively affect total body stores of extracellular citrate even though some of this citrate is ultimately excreted. Parathyroid hormone may simply affect the release of extracellular bone citrate, thereby decreasing total body stores. Such stores could be replenished by vitamin D.

The special significance of citric acid to hormonal and regulatory mechanisms arises from the fact that citric acid enables the body to deal with calcium and phosphate as a single substance or to operate on each of its components singly.

Thus citrate may cause the liberation of calcium phosphate from bone. Under the influence of insulin, such phosphate will be driven into soft tissues and the calcium citrate excreted. On the other hand, citrate can be used to calcify in the presence of phosphate with the partial replacement of phosphate by citrate. The over-all significance of citrate may be related to the fact that calcium and phosphate enter the body as a single unit. Most of this will be deposited as a common material. However, a significant amount of calcium is required for specific reactions not involving phosphorous. A larger amount of phosphorus is also required for reactions not involving calcium. Citrate may thus be looked upon as the catalyst which can bring together, or keep apart, large amounts of calcium phosphate.

Citrate Formation in Bone

The early work of Robison[14] on mechanisms of mineralization of bone indicated that calcification occurs as a result of a reaction of calcium with enzymatically liberated phosphate. Dixon and Perkins[15] have suggested that citrate synthesis by bone has a role in the mobilization and deposition of calcium.

It has been demonstrated that bone contains the enzymes required to synthesize citrate from pyruvate and oxalacetate. Citrate accumulation in bone has been attributed to a lack of isocitric dehydrogenase by Neuman and Neuman.[16] Such a metabolic block would explain citrate

TABLE I—SYNTHESIS OF CITRATE BY BONE HOMOGENATE

Substrate	*mg. % Initial Citrate found*	*mg. % Final Citrate found*
None	2	21
Pyruvate + oxaloacetate	2	28
Potassium citrate	226	202

One ml. of homogenate was incubated with one ml. of the substrate mixture for 30 minutes at 25° under aerobic conditions. The concentration of potassium pyruvate was .05 M, as was the potassium oxaloacetate. Where citrate was used, it was present as 0.1M potassium citrate. The final pH was adjusted to 7.4.

accumulation by bone, since the failure to utilize isocitrate would lead to an accumulation of both citrate and isocitrate.

We have been able to demonstrate a net increase in citrate by an extract obtained from marrow-free femurs of eight week old rabbits. Twenty grams of marrow-free bone were homogenized in 20 ml. of a 0.1 M potassium phosphate buffer, pH = 7.4. The homogenate was filtered through cheesecloth and then centrifuged at 1,000 x g for 20 minutes. All preparative work on the extract was done in the cold.

The data given in Table I indicate that a small amount of citrate is present in the homogenate. We have identified several other organic acids in this extract. Malate and succinate are present. We have also been able to extract considerably greater amounts of citrate from that portion of the homogenate which centrifuges out at 1,000 x g.

The extract is able to carry out a synthesis of citrate from its endogenous substrate as well as from added substrate. This was shown to be enzymatic, since the synthesis could be prevented by pre-heating the bone extract. When citrate was added to a bone homogenate, a small portion of it was metabolized. It would appear that the capacity of the bone to use citrate is actually greater than its synthetic ability. The increases in citrate demonstrated in absence of added citrate probably represent net syntheses. As citrate builds up, the reactions leading to its breakdown are accelerated.

Sodium fluoracetate when added to bone homogenates leads to a marked accumulation of citrate (Table II).

TABLE II—THE EFFECT OF SODIUM FLUORACETATE ON CITRATE LEVELS

Substrate	*Fluoracetate*	*mg. % Citrate found*
None	None	20
None	.05 M	35
P + O.A.A.	None	28
P + O.A.A.	.05 M	45
Citrate	None	202
Citrate	.05 M	256

The conditions of the experiment are described in Table I. The initial concentrations of materials are the same as in Table I. Sodium fluoracetate was added to the substrate, where it was present at 0.1 M.

One would predict such an increased accumulation of citrate only if the tricarboxyllic acid cycle were fully functional in the absence of fluoracetate. Our data are not consistent with the concept advanced by Neuman and Neuman,[16] relating to a metabolic block involving isocitric dehydrogenase. It tends to support the earlier work of Dixon, which emphasizes the presence of the complete citric acid cycle in bone.

One would not predict increased accumulation of citrate by fluoracetate poisoning of the enzyme aconitase if isocitric dehydrogenase were absent or inhibited. Our results are consistent with the concept of Neuman and Neuman only if bone contains enzymes capable of splitting isocitrate prior to dehydrogenation. These enzymes have not been described in bone.

We have not observed the usual lag period required for the action of sodium fluoracetate. Such a lag has usually been described as necessary for the accumulation of fluorocitrate by the condensation of fluoracetate and oxalacetate. The work of Peters[17] demonstrates that fluorocitrate is actually the inhibitor leading to the accumulation of citrate. The present work suggests the possibility that bone may form fluorocitrate as follows:

$$\text{citrate} + \text{fluoracetate} \rightleftharpoons \text{fluorocitrate} + \text{acetate}$$

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SECTION ON MEDICINE

Saturday, March 25, 1961, 10:00 a.m. to 4:30 p.m.

SYMPOSIUM ON*

ENDOTOXINS AND GRAM NEGATIVE INFECTIONS

Morning Session	*Afternoon Session*
IVAN L. BENNETT, JR.	CHANDLER A. STETSON, JR.
ABRAHAM I. BRAUDE	SHELDON E. GREISMAN
LUCIEN B. GUZE	EDWARD W. HOOK

* Supported by a Grant-in-Aid from the Merck Sharp & Dohme Postgraduate Program.

OBSERVED PSYCHIATRIC REACTIONS FOLLOWING USE OF AMPHETAMINE AND AMPHETAMINE-LIKE SUBSTANCES*

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Amphetamine and amphetamine-like substances are sympathomimetic amines whose peripheral adrenergic action is minor but whose central nervous system stimulation is major. These drugs have been widely prescribed to reduce fatigue and suppress appetite as well as to treat depression, emphasizing again their central nervous system effect.[1, 2]

The amphetamines are one of the most widely used groups of drugs.[3] A naturally occurring amphetamine-like substance, Kat, has been used for centuries in Asia and Africa, where it is still popular for its stimulating and euphoriant properties as well as for its appetite-reducing powers. Addictive tendencies to Kat are known, as are toxic effects, including cardiac lesions and impotency.[4] The modern amphetamines were developed for clinical use in 1933. Within a few years they were being extensively used and the first warning concerning their toxic effects were issued. Editorials in the *Journal of the American Medical Association* in 1937 and again in 1938 warned against the indiscriminate use of amphetamine, and reported that the drug was being used at college campuses for cram sessions with resultant fainting, exhaustion and collapse. In 1938 the drug was beginning to be used to treat obesity, with "craving and even addiction" reported. Caution was advised in the use of amphetamine, as the long-range effects of the drug were not yet known.[5-7]

Amphetamine has a rotatory carbon group thus existing in both levo and dextro forms. The dextro form is twice as active centrally as is the racemic "dextro and levo" amphetamine. A third form is methyl amphetamine. These three basic amphetamines in various salts and combinations of salts, and occasionally with barbiturates added, are the three

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basic types of amphetamine prescribed today. Phenmetrazine is an amphetamine-like substance whose action on the central nervous system is similar to amphetamine in producing increased mental alacrity, brighter spirits, euphoria and a feeling of increased energy. The appetite may be reduced by the central inhibition of hunger. Toxic effects include nervousness, irritability, insomnia and toxic psychoses, plus the danger of habituation. Although the first scientific usage of the amphetamines was as a respiratory stimulant, they are little used for this today. Doses of amphetamine far too small to evoke respiratory changes will cause definite stimulation of the sensory cortex. This enormous sensitivity of the central nervous system accounts for both the beneficial and the injurious properties of these drugs.[2, 8, 9]

The amphetamines have been used to treat a large variety of illnesses. At the present time they are recommended for depressed states, narcolepsy, postencephaletic Parkinson's disease, epilepsy, barbital poisoning, drug addiction, alcoholism, obesity and childhood behavior disorders.[3] Although widely advised for use in the treatment of depressed states, several recent authors look unfavorably upon this and state that the side effects of insomnia, nervousness, irritability and possible toxic psychosis make amphetamine less attractive than other antidepressant drugs.[4, 10] The central stimulation produced by the amphetamines is often followed by depression, fatigue and exhaustion, but the desire to sleep does not always follow their use, which may lead some patients to take further dosage of the drugs in order to renew their energy.

The use of amphetamine to improve athletic performance and mental performance at time of examinations has been tested and found to produce little of the desired effect. However, the patients being tested reported a feeling that they were doing better than they actually were. Psychiatric interviews with patients under the stimulation of amphetamine have produced no noteworthy effects and occasionally undesirable symptoms have been exacerbated.[11]

The modern literature is in great disagreement over whether addiction to amphetamines can occur or whether simple habituation, such as to coffee or cigarettes, is the only danger.[3, 12] Recent clinical evidence of withdrawal symptoms and of a high relapse rate in abuse of the drug by addictive persons indicates that true addiction occurs more frequently than suspected. Also, more accurate clinical studies of amphetamine psychoses reveal that many psychiatric patients have been treated for

schizophrenia when actually suffering from toxic amphetamine reactions. Delirious states and convulsions have been reported upon withdrawal of the drug, although withdrawal is most frequently of a benign nature.[9, 13, 14] Abrupt withdrawal and lengthy hospitalization is the most effective treatment.[15]

The clinical picture of amphetamine psychosis is commonly a paranoid psychosis with little or no evidence of drug toxicity. That is, the patient presents ideas of reference, delusions of persecution, auditory and visual hallucinations, but no clouding of consciousness and no typical syndrome of toxic physical signs. This mental picture may be identical with an alcoholic hallucinosis and it usually disappears within a week.[16] The withdrawal phase may be benign, although irritability is a frequent withdrawal symptom. The remarkable similarity of this toxic psychosis to paranoid schizophrenia has been brought out by several authors. It has been repeatedly shown that amphetamines are hallucinogens and may cause psychosis with a single dose as well as with long-term usage. However, individual sensitivity to these drugs varies widely, and some authors have reported the therapeutic use of amphetamine in moderation for up to sixteen years without ill effects.[12]

Patients who abuse the use of amphetamines frequently have serious personality defects, but this is not always evident. Connell feels that "persons liable to become addicted to the drug are not easily recognized".[13] Several authors feel that latent schizophrenia is uncovered or exacerbated by the drug and that paranoid symptoms are only produced in people with paranoid tendencies, while other authors refute this and feel that amphetamine produces a true psychosis by interference with some basic metabolic system which may also be involved in schizophrenia. Certainly the basic personality structure of patients suffering from amphetamine psychosis ranges through psychoneurotic, schizoid and psychopathic.[1, 16-18]

Thirty-one patients observed and treated at the New York Hospital-Westchester Division were found to be suffering from psychiatric reactions following the use of amphetamine or amphetamine-like substances, 17 of them women and 14, men. Ten of the 31 were physicians, one was a nurse, one was a doctor's son and two were doctors' wives, a fact that testifies to the danger of readily accessible drugs. All of the 31 patients had severe personality problems, with depression playing a major part in 17. Final diagnoses included 16 schizophrenic patients,

eight of whom had paranoid trends remaining after remission of the toxic state. Nine patients were diagnosed as having psychopathic personality, and these included two patients with histories of convulsive disorder and confirmatory EEGs. Five patients were considered to have manic-depressive psychoses and one was treated for psychoneurosis. Although all of the patients had some, if not strong, paranoid symptomatology on admission, only five were eventually diagnosed as paranoid schizophrenia and one as a paranoid condition. Psychological studies carried out soon after admission revealed that of the 16 patients tested, 12 had underlying paranoid trends. On one patient a psychological test was repeated some months later, with identical findings of dementia praecox of a paranoid type, which was the final diagnosis. Follow-ups are not complete, but three patients are known to have returned to the use of amphetamine. One of these patients committed suicide within a year after discharge and six patients were reported as doing well for as long as three years after hospitalization.

The 17 women patients had an average age of 37 years, but this obscures the fact that nine were less than 35 years and six were 45 years of age or over. This grouping of the patients into younger and older sections is also true of the male patients and seems to indicate either a lessened resistance to life's stress in these age brackets or the occurrence of greater stress at these times of life.

Seven of the women patients were single, nine were married and one was divorced. Sixteen of the 17 women patients used either alcohol or barbiturates, or both, with the amphetamine. Other sedative and narcotic drugs were frequently used in addition. It is impossible to obtain accurate information on the amounts of medication taken by each patient. However, four patients admitted taking 100 mg. or more of amphetamine each day and five patients admitted the use of 40 to 100 mg. a day, leaving eight of these 17 women patients who stated they took less than 40 mg. a day. Connell states that amphetamine psychosis is unusual with dosages of less than 50 mg. a day. Therefore it seems likely that the patients falsified the amount of drug that they had taken; and in many instances false reports from the patients have indeed been discovered and, in certain instances, subsequently admitted by the patients themselves. This frequent falsifying of dosage levels by the patients may be an indication of the reported loss of insight due to the amphetamines. However, it may also indicate the severe pathology

in these patients' basic personalities. Of the 17 women patients, eight began taking amphetamine for obesity, eight began because of depression and one patient stated, "In order to overcome alcoholism, I began to take amphetamine". The eight women patients who began taking amphetamine for obesity all had depressions associated with their obesity and seemed to eat in response to depression. Many of them subsequently were able to say that they needed the amphetamine as much for their mood as for their weight. Sixteen of the patients took the amphetamine in pill form, several used the Spansule and others took amphetamine combined with barbiturates. One patient admitted using amphetamine in oil as nasal drops as well as amphetamine inhalers. This latter source of amphetamine is now eliminated by the substitution of a different decongestive drug in the inhalers.

One female patient is of particular interest because of the onset of an acute toxic psychosis as the result of a single dose of amphetamine. This women ingested 50 mg. of amphetamine as a suicidal gesture, resulting in agitation and auditory hallucinations that cleared within three days. Shortly thereafter she again took a similar single large dose of amphetamine, causing the same reaction of auditory hallucinations, coupled this time with strong paranoid delusions. She felt that people were going to harm her or attack her sexually, but within a week after hospitalization these acute symptoms subsided. This person had a shy, schizoid personality and was frequently depressed.

The average age of the 14 male patients was 36 years, but again there were seven below 35 years of age, and six were 45 or over. Five of the men were single; eight were married and one had been divorced, thus substantiating the findings seen in the 17 women patients and agreeing with several authors who see marital status as of no relevant value in predicting amphetamine abuse. Eleven of the 14 men used either alcohol or barbiturates, or both, with the amphetamines. One man began taking amphetamine and continued this in amounts of 100 to 200 mg. a day for eight years, with resultant violently assaultive, paranoid reactions. Following hospitalization for this he was able to say, "I went for several months without the drug and was not paranoid". However, because of his depressed state, he began taking an amphetamine-like substance (Phenmetrazine), and again became restless and suspicious and had ideas of reference that led to his second hospitalization at the New York Hospital-Westchester Division. Not one of the 14 male

patients had been taking amphetamine for obesity. Seven began amphetamine because of depression and five for addictive reasons. One had used it as a substitute for alcohol, and one patient stated that he tried the amphetamines as an antidote for barbiturates, to which he was addicted. Eight of the patients admitted using 100 mg. or more of amphetamine a day.

Impotency among males has been reported as a side effect of amphetamine. Only one of the 14 male patients in this series complained of impotency during its use. However, one other patient noted loss of orgasm despite continued ability to maintain an erection. Several patients reported an increase in their sexual desire, and several indulged in elaborate sexual fantasies during their toxic state.

The duration of drug use was less than two years in only three of the 31 patients presented. However, in many cases this was intermittent and would be eliminated at times when the person's mood was naturally elevated, and then the amphetamine would be resumed when the person became depressed.

Following is a case study of a 49 year old married, white female patient, who entered the New York Hospital-Westchester Division with an intermittent six year history of paranoid delusions and olfactory hallucinations. During these six years she had been hospitalized elsewhere three times and each time given a diagnosis of dementia praecox, paranoid type. Each hospitalization was of a week or two in length, and her use of amphetamines was not revealed by the patient. The patient's husband related a six year history of delusional suspicions, including the fear that someone was putting poison in her baby's milk and that he, the husband, had installed a machine in their apartment to remove the oxygen from the air. This caused the patient to keep her windows wide open even in the coldest weather. She complained most bitterly about the peculiar odor in her apartment. This seemed to center about the room draperies, and extravagant cleaning bills were the result of the patient's endeavor to rid her home of her olfactory hallucinations.

Within a week after admission to the New York Hospital-Westchester Division this patient's paranoid trend and delusions disappeared. There were no withdrawal symptoms and although the patient was sleeping poorly, this was not exacerbated at any point during withdrawal, which was abrupt and without substitution of any other drug.

The patient's basic personality became evident as one of a hypomanic nature. At first she had been violently suspicious and hostile toward hospitalization, but she now radiated pleasure at being in the hospital. Whereas she had previously felt that her husband was persecuting her, she now enthusiastically welcomed his visits and encouraged him to think of re-establishing their affectionate regard for each other. She admitted taking amphetamine, but only 5 or 10 mg. a day, "on occasions", instead of the 100 to 500 mg. a day which she later confessed had been her dosage intermittently for the past six years. She stated that she had begun taking amphetamine because of obesity following the birth of her child, and the dosage had increased rapidly as the patient had used the drug to combat her depressive tendencies. She came to enjoy the euphoriant effects of the drug, but found herself in need of larger quantities to combat the depression that resulted as the effects of the drug would wane. These increased dosages produced amphetamine psychosis with symptoms of paranoid delusions and olfactory hallucinations without clouding of consciousness or other toxic signs. The patient was treated at this hospital for a period of nine months, during which time her basic manic-depressive psychosis became increasingly evident but was well controlled without the use of electro-shock. However, following her discharge the patient went into a manic episode followed by a deep depression which necessitated a short readmission, in the course of which the patient again improved. Within a year after discharge she again resumed taking the drugs and has since been hospitalized elsewhere.

The patient's attitude toward her toxic psychosis following its remission is of interest. She had little insight during the more acute phase, but following it she would readily admit her overuse of medication, although she treated this in a light-hearted fashion. She also made little of her delusions and hallucinations and never saw them in any other light than as justified reactions at the time that she entertained them. This tendency of the amphetamine drugs to reduce or abolish insight is common to many of the patients studied here. It has also been reported by other authors.

Discussion

All of the 31 patients in this study presented serious personality problems and 27 used other drugs in addition to amphetamine. Basically,

paranoid ideation was present in a large number of the patients studied and frequently a concomitant depression was observed in the female patients. Paranoid symptoms are common following the use of amphetamines, and occur in schizoids with paranoid personalities as well as in manic-depressives who have shown basic paranoid tendencies. The same is true in psychopathic personalities and in psychoneurotics. It is recommended that patients with rapidly evaporating paranoid symptoms and addictive histories be closely examined for amphetamine abuse. Physicians and people close to the medical profession, as well as obese women with depressive tendencies, all seem particularly susceptible to overuse of amphetamines. Failure to recognize amphetamine as a causative agent in psychopathological conditions makes correct diagnosis and effective treatment difficult, if not impossible.

Treatment consisted of abrupt withdrawal of the drugs and lengthy hospitalization. Many patients were supported during the first week or two with intravenous glucose and insulin and some underwent a gradual barbiturate withdrawal. There were no untoward withdrawal symptoms, although many patients were irritable and some patients maintained their paranoid outlook for several weeks. An incomplete follow-up study shows that a good therapeutic result was obtained in a substantial percentage of the cases. Only three of the 31 patients are known to have again returned to abuse of amphetamine.

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SECTION ON MICROBIOLOGY

Thursday and Friday, March 9 and 10, 1961

SYMPOSIUM ON

FUNGI AND FUNGUS DISEASES

Thursday, March 9

9:00 a.m. THE FUNGUS AS SAPROPHYTE AND PATHOGEN

Chairman: C. W. Emmons. *Speakers:* N. F. Conant, J. C. Gentles, F. H. Theodore, G. Segretain, P. Lavalle, L. Ajello

2:30 p.m. METABOLISM AND GENETICS OF FUNGI

Chairman: E. L. Tatum. *Speakers:* L. Pine, J. O. Lampen, L. S. Olive, G. W. Grigg

Friday, March 10

9:00 a.m. THE FUNGUS AS PATHOGEN

Chairman: C. C. Campbell. *Speakers:* E. G. McNall, R. Brown, H. Seeliger, E. E. Evans, M. A. Gordon, C. H. Binford

2:30 p.m. CONTROL AND TREATMENT OF FUNGOUS INFECTIONS

Chairman: M. L. Furculow. *Speakers:* M. Huppert, H. B. Levine, M. Silva, H. R. Buckley

Panel Discussion on THERAPY

Moderator: M. L. Littman. *Speakers:* M. L. Furculow, C. T. Nelson, C. W. Emmons, W. A. Winn

THE USE AND ABUSE OF TRANQUILIZERS

*Transcription of a Panel Meeting on Therapeutics**

JOHN M. COTTON . . . Moderator

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Panel Members

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Director, Department of Pediatrics, St. Luke's Hospital; Assistant Clinical Professor of Pediatrics, College of Physicians and Surgeons, Columbia University

SIDNEY MALITZ

Associate in Psychiatry, College of Physicians and Surgeons, Columbia University; Acting Chief of Psychiatric Research, New York State Psychiatric Institute; Associate Attending Psychiatrist, Vanderbilt Clinic

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* Presented at the Monthly Panel Meeting (Seventh Series) at The New York Academy of Medicine.

MODERATOR JOHN M. COTTON: Our topic for discussion this afternoon is "The Use and Abuse of Tranquilizers". The medical history of the past few decades includes many instances of the discovery of new drugs which have been introduced and accepted with wide-spread enthusiasm by the public, both medical and lay. However, after a time, when the initial excitement has subsided, it has been possible to assess rationally these drugs and to assign them their proper places in the pharmacologic and therapeutic armamentarium of the physician. This series of events has certainly been true as far as the tranquilizers are concerned.

Also, a certain amount of confusion has been added as a result of the multiplicity of new preparations introduced at frequent intervals by various pharmaceutical manufacturers. Each of the products has its own distinctive, registered name, but may often have the same, or similar pharmacologic action as drugs already available. It would appear that some of these products are supported by quite inadequate experimental work and clinical trial.

However, the tranquilizers include important groups of drugs, and since our time is limited, we shall restrict our discussion to representatives of four main groups: the rauwolfia alkaloids, the phenothiazines, the propanediols (Meprobamate) and the monaminoxidase inhibitors.

As you will note on the program, our panel is representative of a rather broad area of medical interest, both clinical and research. It includes an internist, a pediatrician, an anesthesiologist, and a psychiatrist. The last is not only a clinician but is also deeply interested and involved in experimental work with these drugs.

I shall ask Dr. Sidney Malitz to open the discussion.

DR. SIDNEY MALITZ: We don't have sufficient time to discuss every drug individually, so I shall pick one from each group as the prototype and discuss it in greater detail.

There are four major groups: the phenothiazines, the rauwolfia alkaloids, the diphenylmethane derivatives, and the substituted propanediols. At this point, you might well ask, what is a tranquilizer and how does it differ from some of the conventional central nervous system depressants, such as the barbiturates, paraldehyde or chloral hydrate? The term "tranquilizer" has been much maligned. Barbiturates and other sedatives have sometimes erroneously been called "tranquilizers". A true tranquilizer is a drug capable of effectively reducing

marked anxiety, motor hyperactivity and, in some instances, bizarre or assaultive behavior, without also markedly lowering the level of conscious awareness; in other words, without making the patient very drowsy or putting him to sleep. The advantages of such drugs over the previously mentioned central nervous depressants then become obvious. First, they reduce excessive motor activity and anxiety without "knocking out" the patient; and secondly, they facilitate communication with the patient since he becomes more accessible by remaining awake and calm at the same time. These characteristics of the tranquilizers have made it possible to approach psychotherapeutically for the first time certain previously violent and destructive patients. In the past, such patients were usually hospitalized, kept in restraints and, if uncontrolled by these measures, given large doses of barbiturates or other sedatives which often would make them very drowsy or put them to sleep and, in some instances, would produce clouding of consciousness and transient disorientation and confusion.

Considerable recent research has been devoted to where and how these new drugs act. The complete answer has not yet been found. It appears that they act on subcortical areas, in the neighborhood of the diencephalon, hypothalamus and reticular substance, as opposed to the barbiturates, which act more directly on the cortex. The hypothalamus has come into much prominence of late, as the "seat of the emotions". Future research will probably clarify further its role in connection with affective disturbances. The reticular substance in the brain stem is concerned with the awakening and alerting mechanism. It, too, is receiving a great deal of attention in current research. The "how" of these drugs' actions is still unclear. Recent work has produced evidence that the catechol amines, which include serotonin, epinephrine and nor-epinephrine, are concerned with brain functioning and are probably involved in synaptic transmission. It is postulated that alterations of the levels of these substances in the brain may result in disordered behavior.

Reserpine releases serotonin from its depot sites in the brain, thus altering the concentration of serotonin present. Serotonin, epinephrine and nor-epinephrine are destroyed by the enzyme monoamine oxidase. Some of the new anti-depressant agents such as iproniazid (Marsilid) inhibit the action of monoamine oxidase. This, in effect, serves to *increase* the level of catechol amines in the brain. Whether such measurable changes in the concentration of these brain substances are causal, or

merely an accompanying phenomenon to behavioral changes, has not yet been definitely established.

Clinically, the most effective all-around tranquilizer is chlorpromazine (Thorazine), the first member of the phenothiazine group to be used in psychiatric treatment. Although this drug has many associated side effects, few are serious and the drug is surprisingly safe over-all, considering that it has been prescribed for literally millions of people throughout the world. More will be said about its side effects later. Since reserpine (Serpasil) has similar clinical indications, I shall discuss these two drugs together, although reserpine is the chief member of a different group, the rauwolfia alkaloids. Because there is usually several days' to a week's delay before reserpine begins its action, while chlorpromazine works almost immediately, there has been a greater tendency for clinicians to use chlorpromazine, especially in acutely disturbed and hyperactive patients. Both drugs have numerous derivatives. The 3-carbon straight side-chain derivatives of chlorpromazine and those with a fluorine radical seem to be much more potent, milligram for milligram, but they also have a much higher incidence of side effects, especially those involving the extra-pyramidal system. Research today with these drugs aims at finding compounds which have the most marked clinical effects with the least side effects on the smallest possible dosage.

What are some of the clinical indications for chlorpromazine and reserpine from the psychiatrist's viewpoint? In considering this question, it is more fruitful to think of "target symptoms", a term coined by Dr. Fritz Freyhan of the Delaware State Hospital, than diagnostic categories. In other words, what clinical symptoms are best relieved by these drugs?

Marked, severe anxiety is the first symptom for which these drugs are effective, especially when accompanied by hyperactivity. Because of the side effects associated with these drugs, they should not be used for mild anxiety or in situations where the patient is making an adequate adjustment in the major life areas—sexual, social and work. Milder forms of anxiety are still best treated by barbiturates or meprobamate. Phobic symptoms in a patient may show a paradoxical response. Some phobic patients may become more phobic about the side effects associated with the drug, and discontinue taking it. The phobic patient who cannot travel to the doctor's office because of his fear of travelling

by car, train or bus may, with chlorpromazine or reserpine, be able to get to the doctor's office for psychotherapy or other psychiatric treatment. In such patients, the drug is very helpful. But one cannot always be sure of the response until one actually tries the drug on the individual patient. Obsessive-compulsive symptoms do not respond well to tranquilizers. Patients with such symptoms may become obsessively preoccupied with the subjective sensations they experience from these drugs and actually become worse. Acute psychotic symptoms, such as hallucinations and delusions, may subside or diminish when patients suffering from these symptoms are given chlorpromazine, reserpine or their derivatives. This is most likely to occur, however, only when these symptoms are accompanied by considerable anxiety and hyperactivity. The so-called "burnt-out", withdrawn psychotic patient usually does not show any alteration in the hallucinations and delusions from which he suffers. The more a patient is reacting to his hallucinations or delusions, in other words, the more he is fighting back, the better is his chance of some relief with these drugs. Acute psychotic reactions associated with alcoholism and the withdrawal state after drinking has been stopped, have responded favorably to these drugs.

What are some of the side effects seen with chlorpromazine and reserpine? They can be roughly divided into physiological and psychological. Among the common and relatively harmless physiological side effects are feelings of fatigue or weakness, nasal stuffiness, dry mouth, diarrhea or constipation and occasional dizziness. Hypotension can also occur, more in older patients, and usually postural in nature. More serious is the jaundice which has been seen with chlorpromazine but not with reserpine. Fortunately, it appears to be an obstructive jaundice and does not involve the liver parenchyma. It reverses itself, usually several weeks after the drug is discontinued. Occasionally, it must be differentiated from a possible surgical emergency. The more recent phenothiazine derivatives have shown a much lower incidence of jaundice and at least one, Trilafon, has not had any cases of jaundice attributed to it to date. The possibility of more cases of jaundice developing with these new derivatives, as more experience with them is gained, should not be ruled out. Both chlorpromazine and reserpine are associated with extrapyramidal side effects. After prolonged administration, a Parkinsonian picture may develop, with mask-like facies, drooling, oily skin, flexion of the extremities, cog-wheel rigidity and pill-

rolling. This, too, disappears when the drugs are discontinued or, in some instances, where the dosage is lowered and anti-Parkinson agents such as Artane or Parsidal are administered. More acute extrapyramidal effects are extremely interesting and may prove both puzzling and alarming when first seen, if the physician has not been forewarned of their occurrence. The first group, the *acathisias*, are symptoms of hyperactivity consisting of marked restlessness and inability to sit or stand still. The patient complains of feeling very anxious and tense and may say he feels like jumping out of his skin. Some physicians may mistake these for the patient's own basic symptoms and give even more of the offending drug, which, of course, will make the symptoms even worse. When these side effects develop, the patient should have the drug stopped or reduced, and a barbiturate administered at once. *Dyskinesias* also develop after a short period on the phenothiazines and may be confused with hysterical reactions. Patients may develop bizarre posturing, opisthotonus, rhythmic extensor and flexor spasms of the extremities, spastic torticollis, involuntary protusion of the tongue and oculogyric crises, with the eyeballs rolled upward and outward. These phenomena can be extremely frightening to both the patient and the observer. They are more common with the newer, more potent phenothiazine derivatives. I have especially noted them to occur when a physician, not completely familiar with the dosage of a new phenothiazine, starts the patient on a dosage much higher than recommended, confusing it with the dosage of chlorpromazine. I have found that an intravenous solution of 250 mg. of sodium amobarbital (Sodium Amytal) in 10 ml. of water, administered at the rate of about 2 ml. per minute, is extremely effective in controlling these side effects.

Agranulocytosis has been occasionally reported with the phenothiazines. Its presence is always serious. It may be ushered in by signs of a sore throat. Since Dr. Rosenfeld will undoubtedly go into greater detail about the recognition and treatment of medical side effects later, I shall say no more about them at this time. I would like to say a word further about the psychic side effects, however. Depression occurs occasionally with reserpine administration, and may be severe enough to result in suicidal attempts requiring hospitalization and treatment with electro-shock. Understandably, then, these drugs should not be given to patients already depressed. Depersonalization phenomena have been known to occur with both chlorpromazine and reserpine, some-

times becoming so severe that acute psychotic reactions develop. Discontinuing these drugs usually results in a quick remission within 24 to 48 hours.

These side effects underscore the importance of administering these drugs under careful supervision, giving serious consideration to the indications for their use. They are not to be used lightly. They should not be given to the patient the way a placebo might be given to stop his complaints. There is no rule of thumb as to dosage. Some patients obtain satisfactory clinical responses on very low dosage; others require very high maintenance levels. Side effects may develop after a relatively small amount of drug or may not appear even on extremely high doses. Some patients develop a tolerance, while others can be maintained for long periods or even have the dose level reduced, with little appreciable loss in clinical effectiveness.

Meprobamate, marketed as Miltown and Equanil, outsells all the other so-called tranquilizers put together. Actually, it does not belong in the "major tranquilizer" group, a term reserved for the phenothiazines and rauwolfia alkaloids. In patients with milder anxieties it seems to have some effect, but it is still not certain whether this effect is superior to that of a mild barbiturate such as phenobarbital. There are few unpleasant or serious side effects with this drug, although recently instances of habituation and withdrawal reactions have been reported with its use. Non-thrombocytopenic purpura and allergic reactions have also been recorded, but they are rare.

The diphenylmethane group, of which Frenquel is one of the earliest and best known members, has been clinically disappointing. Originally recommended for the treatment of hallucinations, this drug has not justified the initial expectations in later follow-up studies. Atarax is another member of this group which is mild in its effects on anxiety and has also proved disappointing.

Dr. Cotton has mentioned that we would discuss a monaminoxidase inhibitor, iproniazid (Marsilid). Although in isolated instances this drug has had a spectacular effect in relieving depression, it is a dangerous drug and quite toxic. Several deaths, ushered in by jaundice, have been associated with its administration. Unlike chlorpromazine, iproniazid is associated with an involvement of the liver parenchyma, and a microscopic picture identical with acute yellow atrophy. Severe hypotensive reactions are also associated with this drug, resulting in sudden "black-

outs" with occasional injury to the head or extremities during a fall. The treatment of choice for depression remains, at the moment, electric shock treatment. Perhaps we may see derivatives of this drug or related drugs which are not so toxic and even more effective against depression, at a later date.

In summary, then, these drugs certainly have a use in the treatment of mentally ill and emotionally upset patients. They are not curative but help to reduce quantitatively a number of the patient's distressing symptoms, enabling him to utilize more effectively his remaining adaptive resources and affording him greater relief from suffering. They are not a substitute for psychotherapy. Rather they are ancillary to it. They should always be used with caution and under constant supervision. Even then, they should be reserved for the severest emotional disturbances. When patients are not responsive to these drugs, it would probably be best to refer them to the psychiatrist for further evaluation and treatment.

MODERATOR COTTON: We shall now ask Dr. Lester C. Mark to discuss these agents from the viewpoint of the anesthesiologist.

DR. LESTER C. MARK: Tranquilizers were introduced into anesthesiology long before they were recognized or titled tranquilizers. Laborit and Huguenard in Paris first brought the use of artificial tranquilization to the fore. They used drugs that we now know as tranquilizers to produce a state of artificial hibernation. This was a revolutionary concept, although the chief merit of the procedure was that of hypothermia.

A second revolution came about more recently, but was somewhat more abortive. Last year in South Africa, Dr. Hayward Butt used the word analgesia to describe the state of ataraxia produced by Pacatal in combination with analgesia produced by large doses of meperidine and a narcotic-antagonist, Daptazol, to perform minor surgery and even some major procedures in ambulatory and semi-ambulatory patients. Unfortunately, our experience with this combination of drugs was disappointing. We were unable to achieve the ataractic state without severe depression of the patient's state of consciousness, and the analgesia obtained was also unsatisfactory. We gave up using this combination of drugs. Dr. Butt passed through New York a few weeks ago. We discussed this problem with him and we all agreed that more work on assessing this drug was necessary.

However, there may still be a useful place for the tranquilizers in anesthesia. What are the possibilities? Obviously, if these drugs are tranquilizers, they should tranquilize, and where better to apply this than in the patient who is about to have an operation, and particularly an anesthetic—terrifying things both. It has been suggested that we can tranquilize not only the patient's psyche with these drugs, but also his soma, reducing reflex irritability and, in general, enhancing the anesthetic state. The effect is further augmented by the potentiating action which many of the tranquilizers have. This is particularly true of the reserpine group, and also of the phenothiazines; it is somewhat less true of the diphenylmethanes, although some of these do have potentiating action.

What this means is simply that we get "more mileage" out of the other drugs, particularly the narcotic drugs and the hypnotics (such as the barbiturates) used for preoperative medication and during the anesthesia itself. There is less of a potentiating action on the inhalation agents such as cyclopropane and ether. However, this potentiation is present in the preoperative period, so that we may use fewer drugs before the anesthesia. Also, smaller doses of drugs are required in the postoperative period, at least early, so that the postoperative requirement for analgesics is reduced. Finally, it has been suggested that tranquilizers be used in the treatment of nausea and vomiting, hiccoughs and emergence delirium.

What happens when we attempt to exploit these suggested properties? First, by and large we tend to get a considerable amount of depression, and I am not speaking about the psychiatric variety now, but the physical depression, the sedation, depression of blood pressure, respiration, and so on, with a delayed awakening from anesthesia in many cases. I don't suggest that this always happens, but it is something we see often enough for us to be concerned about it. The depression of the blood pressure is particularly significant and particularly disturbing. It should be remembered that these drugs potentiate the action of narcotic and other sedative drugs which, of themselves, can produce hypotension. We also have the hypothalamic depression that Dr. Malitz referred to. This is particularly true with the phenothiazines. These produce not only hypothalamic depression, which is the equivalent of sympathetic nervous system depression, but also have a definite anti-epinephrine action. This adrenalytic action means that hypotension

will generally respond poorly to vasopressors. Epinephrine particularly is a bad choice of therapy, because its ordinary hypertensive response is blocked, and one can instead have an epinephrine reversal and an aggravation of the hypotension. Ephedrine and other lesser vasopressors are not very effective, and it actually takes rather large doses of such potent vasopressors as Neosynephrine and Levophed to counteract this kind of response.

Coakley and co-workers described in the *J.A.M.A.* a few years ago the adverse circulatory effect of rauwolfia therapy on those who came for operations; and in a group of 40 patients they reported serious hypotension in 16. One of these was simply the result of preoperative medication before anesthesia had started; in the other 15, the hypotension occurred during the surgery and anesthesia, and in all of these there was a poor response to vasopressor therapy.

The potentiating action of these drugs is worthy of emphasis, since it can be rather insidious. We may have a patient in whom the sedative effect of a hypnotic drug or the depressant action of a narcotic drug has apparently worn off; however, the drug has not been entirely excreted, and if we now give one of these tranquilizers, we have a subthreshold amount of the original drug in the body which is potentiated, and we may see again the appearance of a depressant response in the patient. This can be of serious importance. For example, in our recovery room, a postoperative patient was hiccoughing; he had had severe hiccoughs for half an hour. Someone saw him and said: "So! let's give a small dose of chlorpromazine." He was given 12.5 milligrams intravenously, not a very large dose. Shortly thereafter someone asked: "By the way, did you know that he was given 25 mg. of meperidine just prior to the end of surgery?" Well, this wasn't in the record. Somebody had committed an oversight. Fortunately we were alerted, because very shortly thereafter this patient developed a severe hypotension, a temporary apnea, and if we had not been quite prompt in our resuscitation, this could have resulted in a tragedy. So, potentiation can hit us in many ways.

We should also mention that there are local irritant effects of these drugs, when used intramuscularly and intravenously, which is how we usually give them in anesthesia. The phenothiazines, as a class, seem to be responsible for this kind of response. Patients receiving Pacatal intramuscularly frequently complain of a burning on injection and may

show induration, redness and, occasionally, a mild necrosis and slough afterwards. An article in a recent issue of the *J.A.M.A.* describes two cases of what was termed arterial thrombosis and gangrene following the intravenous injection of Pacatal, given into the antecubital space. The patient immediately reported pain in the hand and fingers and subsequently developed arterial spasm, which required amputation of the hand. I might point out that the interpretation here is questionable. It is fairly obvious that this was intra-arterial rather than intravenous injection. This is an irritant drug, something we should remember.

I won't mention the other side effects to which Dr. Malitz has already alluded.

What precautions should be taken with patients on these drugs who are to be anesthetized? The most important single thing I can urge upon all of you is to *communicate*—inform the anesthesiologist, the surgeons, and others responsible for the patient's care, what medication he has been receiving. It is important that the anesthesiologist know what drugs the patient has been receiving. The recovery room episode that I mentioned previously was a failure of communication. Fortunately, it was just delayed; it wasn't completely cut off. So, please, communicate!

In the patient who is already receiving one or another of these drugs, we must decide whether we should stop the drugs preoperatively. We must decide whether the patient must have tranquilizing therapy for his hypertensive state, and if it is feasible to eliminate this for a period of time before, during and after surgery. The period of time will depend upon the drug. Stopping the drugs for two or three days may be quite enough for the phenothiazines and the substituted propanediols; it is not enough for the rauwolfia alkaloids. The serotonin stores in the body are depleted after administration of the rauwolfia compounds. It takes eight to ten days for them to be fully restored, and that means we should stop rauwolfia therapy some ten to fourteen days ahead of time to guard against the hazard of serious circulatory depression during surgery. We should avoid combinations of the tranquilizing drugs with such forms of anesthesia as spinal, epidural and caudal. Notice that all of these involve sympathetic blockade. Patients on rauwolfia compounds and the phenothiazines may show evidence of sympathetic blockade. It may not be apparent. But, if on top of this, a

chemically induced block for surgical anesthesia is added, the result can be disastrous.

Finally, we should use minimal doses of other depressant drugs, in pre-medication, in anesthesia, and in the early postoperative period of patients who are receiving these tranquilizers, again because of the potentiating action mentioned above.

What is the present status of these drugs? The obstetricians have largely given them up, for two reasons: First, acute hemorrhage is forever a problem in obstetrics, and patients on tranquilizers tolerate blood loss poorly. These patients have a serious hypotension, which responds poorly to vasopressor therapy, as mentioned, and these problems are just too great to cope with. So, except in seriously disturbed patients, the obstetricians are extremely reluctant to combine tranquilizers with other therapy the patients receive. Secondly, the obstetricians are concerned about excessive post-partum depression in the mother, which at times is also a serious problem.

In surgical anesthesia, we have experimented with various tranquilizers for pre-operative medication. We have adopted one that is a sort of stepchild among tranquilizers, that is, promethazine (Phenergan), which is a phenothiazine; but it is more an antihistaminic than a tranquilizer. Promethazine has some usefulness as a sedative, as a potentiator, as a drying agent, and as an antihistaminic. It helps control nausea and vomiting postoperatively. Here is the most useful place for tranquilizers at the present time: in the postoperative state. Nausea, vomiting and hiccoughing will all respond to the tranquilizers, particularly the phenothiazines. But I should point out that we have been unable to produce reversal of any of these conditions without also producing sedation in the patient. Whether this is a potentiating action on the drugs already used, or a direct sedative action of the tranquilizers themselves, I am not prepared to state; but, certainly, we have not been able to separate these effects.

As new drugs appear, it will be claimed that each is more potent and less toxic than the ones we have now. Only time will tell whether these claims are justified. At present the status of the tranquilizers in anesthesia seems rather peaceful!

MODERATOR COTTON: I wish to emphasize one point which, I think, deserves emphasis. Communicating information about drugs that patients have been receiving is especially important for the psychiatrist.

By the time patients get to the psychiatrist, most of them have been given at least one or more of these drugs. I don't recall any patient that has been admitted in emergency to the psychiatric service of St. Luke's Hospital in the last two and a half years who hadn't been receiving rather large doses of one or more of these drugs. So, we always ask, not if they are taking any drug, but what they are taking, and how much.

Some of you may be aware that, in recent years, there has been an increasing interest in the use of these drugs in certain types of problems found in children, and their importance in pediatric practice has not been made fully clear. I think this aspect may be an increasingly interesting one, and it is also an area in which the abuse or improper use of these drugs may be most harmful. I shall ask Dr. J. Frederick Eagle to discuss this problem.

DR. J. FREDERICK EAGLE: Judging by conversations I have had with my pediatric colleagues throughout the country, the use of tranquilizers in pediatrics is quite extensive. Unfortunately, the practicing pediatrician has not written much about his experience, and therefore the literature on the use of tranquilizers in children is rather sparse and comes, for the most part, from institutions where severely disturbed or mentally retarded children are being treated.

On the other hand, in so far as the abuse of these drugs is concerned, Dr. Lauretta Bender stated in this meeting-room last evening* that no deaths have been reported from the use of tranquilizers in children, and in my search of the literature I was unable to find any fatality report. I think that at the moment any abuse of tranquilizing drugs for children has not yet become apparent.

I would now like to speak briefly about some of the organic disorders for which tranquilizers are definitely indicated. For the hypertension secondary to acute nephritis, the anti-hypertensive effect is more important than the tranquilizing effect, though the latter complements the former. The drug of choice in this instance is reserpine, but it must be given intramuscularly or intravenously. Fortunately, it is unusual for these patients to over-react and develop a hypotension; in other words, this is really an anti-hypertensive drug rather than a hypotensive drug. The dosage is between 90 and 150 micrograms per kilo or, for the average child in the age group that acquires acute nephritis, about two or three milligrams per day. The effect is noticeable

* Meeting of the Section on Pediatrics, New York Academy of Medicine, *Experience with drug therapy in a children's unit* (Creedmore State Hospital), Discussion: Lauretta Bender.

within two or three hours, and is greatest in those children with the highest hypertension. The drop in blood pressure will vary between 20 and 50 millimeters of mercury. In a small percentage of cases, an adequate drop in blood pressure is not obtained, and then the use of hydralazine (Apresoline) is very effective in supplementing the effect. For chronic hypertension in children, it is advisable to treat with parenteral and oral reserpine for a three week period of time, after which the parenteral administration can be stopped.

A second, rather rare condition, in which these drugs are useful, is infantile convulsions occurring in infants under one year of age. The drug effects a massive muscular relaxation. The EEG is characterized by three per second waves as compared to the two per second waves found in *petit mal*. To date there has been no effective anti-convulsive treatment for this particular condition. Meprobamate has been tried and found partially effective in 20 per cent of the patients studied. Although this is not a very startling cure or control rate, it represents a tremendous advance in the treatment of a condition for which no treatment existed previously.

A third condition is Sydenham's chorea, associated or unassociated with rheumatic fever. Meprobamate should be the drug of choice, since the action is peripheral and tends to be relaxing. The dosage is variable, between 400 and 1600 mg. per day. In my personal experience with a few cases during the last year, I have not been impressed with the results. I could not be convinced that the drug was affecting the disease. One patient, a seven year old girl, with her second attack of chorea, was started on meprobamate at 100 mg. three times a day. The dosage was increased until she was getting 2400 mg. a day, and at the end of six weeks she was better. I was not persuaded that we were not witnessing merely the natural course of the disease in this particular child. However, this drug certainly deserves a trial.

A fourth area where tranquilizers are used most extensively is in non-specific vomiting. My house staff tells me that there is "nothing, but nothing" like prochlorperazine (Compazine) to stop vomiting and, as you know, in pediatrics vomiting is a most common complaint. In the literature, there are more reports on the use of chlorpromazine than on the use of prochlorperazine. It is estimated to be 80 per cent effective for vomiting associated with infection, following irradiation, and a variety of other causes. The dosage recommended is three milligrams

by rectum or two milligrams by mouth, if the child can keep it down; if not, the dose may be repeated immediately by mouth, or 0.05 mg. per pound may be given intravenously.

An interesting report reveals that the use of chlorpromazine in three cases of pyloric obstruction was ineffective. To me this is rather reassuring, because it suggests that in the case of organic obstruction, the use of these drugs will not disguise the symptomatology of a condition that may require surgery. Whether this will prove to apply to other obstructive lesions has not been determined.

Another condition which some of you may occasionally encounter is that of dysautonomia, which responds well to chlorpromazine. Still another state for which pediatricians have used tranquilizers extensively is the so-called "three-month colic" and the "fussy" baby. Again, there are few published reports. Two that I read recommend tranquilizers. One recommended the use of reserpine at one tenth of a milligram three times a day. The other stated that meprobamate was the drug of choice when given in dosage of between 50 and 200 mg. three times a day. Meprobamate should be the more effective and safer drug. Reserpine takes too long to act, unless given parenterally.

Finally, we must speak of the effects of these drugs on the behaviour of children. You have all had experience with the child that "only a mother could love". Actually, even the mothers of these children don't find this easy, and other evidence suggests that there is a great deal of subconscious resentment towards the hostile, aggressive, and compulsive child. At times, the child and the mother seem to react adversely to each other, and with increasing intensity as the child becomes older.

Here is a major indication for the use of tranquilizers by the pediatrician and the general practitioner. These drugs should not be used when the behavior is so abnormal as to require the services of a psychiatrist, nor are they indicated when the deviation is so mild that it might be considered a phase of normal development. If these children can be "toned down" so that the adult population is not continually fighting with them, in a word, if they can be made lovable, then at least they will not have to struggle against what is basically a hostile environment.

Secondly, they will gain confidence. Many of their anxieties will disappear, and it will no longer be necessary for them to attract adult attention and adult reaction by abnormal or impulsive behavior. In

combination with a sympathetic environment, great progress can be made in a short period of time.

Which tranquilizers should be used under these circumstances? Chlorpromazine (Thorazine), which has been most extensively studied, works the best on those children that are the most seriously disturbed. However, if chlorpromazine is really required, this child is pretty close to being placed in an institution. It is not effective for the milder behaviour reactions, such as nail-biting, temper tantrums, head-banging, and so forth. For these more or less minor behaviour reactions—I say "minor", but they may be very distressing to the parents—we would suggest starting with diphenhydramine (Benadryl). The usual antihistaminic dose may be effective, but if it is not, the dosage should be increased to as high as 400 mg. a day. The toxic effects of diphenhydramine are negligible. This drug is particularly good for calming down a child, or having him stop his impulsive behaviour. It is excellent for headbanging and teethgrinders, nail-biting and night terrors. A word of warning! With high dosage, the elixir cannot be used, because of the high alcohol intake!

I would like to point out that any individual tranquilizer will be effective only in a certain percentage of these children. If diphenhydramine does not accomplish the desired result, I would try meprobamate which, as has been pointed out, is the least toxic and has the fewest side effects. Meprobamate is particularly effective when there is much tension. The child with cerebral palsy who will not walk may make a great deal of progress in a few weeks, as soon as he is released from his fear of falling, and from other tensions and apprehensions. A similar effect may be obtained occasionally in stutterers and in children that are reluctant to face the problem of going to school. Reserpine has limited usefulness, since particularly the side effect of excessive nasal stuffiness makes this drug rather unpleasant. If these drugs are not effective, at the present time I see no contraindication to trying chlorpromazine. However, for severe behaviour reactions, psychiatric consultation is most advisable, in an attempt to determine the underlying source of the condition.

Finally, I would like to speculate for a moment. It seems to me that behaviour reactions in children are not one-way streets. I am sure that many times all of you have thought to yourself, and possibly joked to your confreres, that the phenobarbital should have been given to the

mother. I have no evidence to support this, but I feel fairly certain that many of these children might respond very well if the parent were given the tranquilizer.

MODERATOR COTTON: I think it is clear from day to day clinical practice, that this individual reaction to dosage is very important in children. In all these various areas that Dr. Eagle has spoken about, it is difficult to generalize and be sure that one will get a real tranquilizing effect, or a decrease in the hyperactivity which one sees in some of these children. The quieting effect is quite marked in some, but not in others. In a recent case of Sydenham chorea, I gave rather large doses of meprobamate to diminish excessive activity, with considerable success. However, as Dr. Eagle said, this by no means happens in all such cases.

As the representative of the specialty of internal medicine, I shall call on Dr. Isadore Rosenfeld.

DR. ISADORE ROSENFELD: My colleagues have been so thorough in their discussion of this problem that I am afraid they have left me but little to say.

It is very difficult, in so brief a period, to discuss in any detail the many problems that are raised by the use of tranquilizers in the broad field of internal medicine. If, perhaps, I can leave with you some thoughts and later in the meeting answer some specific questions, I shall have served my purpose.

It is clear from the foregoing presentations that these drugs find their greatest use in the field of psychiatry. At the same time, I have recently been told that one out of every three prescriptions written in this country was for a tranquilizer. I am also told that in a recent year three billion tablets of meprobamate were consumed. Either we are a very nervous nation, or these drugs are being used without reason; and I suspect that this latter statement is true.

Some of the main thoughts that I would like to leave with you are these: That the widespread acceptance of the "miracle pill for the mind," as being harmless therapy for whatever ails one, is a fallacy. All these drugs are powerful and are not without their toxicity. Because of the advertising by the drug manufacturers and, in addition, as the result of the zeal of many clinical investigators in rushing into print with a report of the great new features of some drug, we are often tempted, on the strength of a glowing preliminary report, to use many of these agents long before they have been time-tested and proven. I

would like to remind you that hepatitis, which today is commonly known to be one of the complications following chlorpromazine therapy, was not reported until two years after the initial use of the drug in Europe.

I would also like to emphasize that before any of us uses any drug, for whatever reason, we should really revert to our medical school thinking and learn its indications, contraindications and dosage, learn its action, in so far as it is known, try to delineate its limitations, and also try to anticipate whatever side effects may arise from its use.

In the broad field of internal medicine, I can think of three major areas in which the tranquilizers may be used. The first is the patient who presents, without organic disease, a variety of psychosomatic complaints which are not deemed sufficiently disabling to warrant psychiatric care. This, I think, is the largest group found in the practice of most internists and general practitioners.

The second group of patients to whom one is tempted to give tranquilizers are those who have organic disease of one kind or another but who have, in addition, a strong psychogenic overlay. One example is the cardiac patient who is neurotic or emotionally unstable and who literally goes to pieces when you tell him he has heart disease. His anxiety complicates your management of both the heart disease and the patient.

The third area in which these drugs can be used is in the treatment of specific organic syndromes. An example, of course, is vomiting. I will deal with this in a moment.

Bearing these specific areas of application in mind, let us first consider the phenothiazine group of drugs. I wish to say at the outset that I think there is very little indication for the long-term use of any of the phenothiazine derivatives by those of us who are not psychiatrists. If, in your opinion, somebody really needs chlorpromazine for extended periods of time, I do think that the benefit of a psychiatric opinion should be obtained.

Some of the toxic effects of many of these agents in the phenothiazine group have been mentioned. I would like to discuss for a moment the problem of hypotension. Some of the newer derivatives are being advertised as being free from hypotensive effect. But I would suggest that one take all these claims with a grain of salt. Hardly a day goes by that a medical journal doesn't appear with new case reports

describing a host of toxic effects from every one of these so-called benign drugs. I think, especially in the phenothiazine group, that one ought to consider each of the agents in this group as being at least potentially hypotensive.

Granting that these drugs are potentially hypotensive, in what two areas must one be extremely cautious in their use? The first is in older people, whose compensatory mechanisms for maintaining blood pressure are already somewhat impaired. In an elderly person, the administration of chlorpromazine, followed by a precipitous drop in blood pressure, may induce cerebral thrombosis and the signs of a stroke. I would certainly be cautious about using these drugs in the aged.

The other specific area where one must be alert to the occurrence of hypotension, is in the cardiac. In managing a case of acute infarction, where the patient is vomiting, perhaps due to morphine, or perhaps for other reasons, it is frequently tempting to treat this vomiting with prochlorperazine (Compazine) or chlorpromazine (Thorazine) and so on. I think that one ought to steer clear of these drugs in such a situation, because acute vascular collapse can and does follow the administration of the phenothiazine derivatives. One might better use more benign agents, such as Dramamine or Bonine for the vomiting. The barbiturates and narcotics should be employed for sedation, instead of phenothiazine drugs. I think their prime use in medicine is as anti-emetics over the short term, for an acute gastrointestinal situation. I agree with Dr. Eagle that, in my experience, there is no drug to equal their effectiveness in this field.

The phenothiazines may also be used in those patients in whom long-term sequelae are of no consequence—patients with advanced uremia who vomit, patients with terminal carcinoma in whom narcotics do not seem to control the pain, and in whom one wishes to alter the nature of pain perception. These are the classic, the only indications that I know of, in which it is permissible to use these drugs over a long term.

Internists and general practitioners must learn how to use the phenothiazine derivatives because among office patients to-day there are many who ordinarily would be managed in a mental hospital, but who can be treated on the outside because they are receiving phenothiazine. Every now and then we are called upon to increase the maintenance dosage because of an acute crisis, or reduce it because of toxicity, and

we should be familiar with their side effects. Among these, of course, are hypotension, tachycardia and jaundice. It is true, as Dr. Malitz said, that most cases of jaundice are benign. But there have been reported instances of cirrhosis following so-called benign cholangiolitic hepatitis. You have all seen the variety of skin rashes that can occur and that may be troublesome. Agranulocytosis has been reported. I suppose its incidence is no more than one in ten thousand. If yours is the one, that's a high incidence. The incidence of Parkinsonism is said to be as high as 10 to 50 per cent in some patients receiving the phenothiazine derivatives in large doses over long periods of time.

I shall pass lightly over the rauwolfias, saying only that they may have troublesome side effects, stuffy nose, bad dreams, and so on. But, one should also remember, Parkinsonism is not an infrequent complication of rauwolfia therapy over the long term.

What about the diphenylmethanes: Atarax, Benactyzine, Frenquel, and so on? These, as has been intimated today, are very mild, and if you are looking for a mild sedative, and for some reason you prefer not to use a short-acting barbiturate, you can use one of these. The prototype of this group is Atarax. If you read the medical advertisements in most journals, you know that Atarax is "good for whatever ails you". It is an antihistamine, and it is a sedative, if you need that.

I think a word should be said about the effectiveness of this drug as an antiarrhythmic agent. From my own experience, I would think twice about abandoning the time-honored agents in the treatment of ventricular tachycardia. I can think of no situation in which one would hesitate to use quinidine and give Atarax in its place, except, perhaps, extreme sensitivity to quinidine. Also, the literature supporting the use of Atarax (hydroxyzine) as an antiarrhythmic seems somewhat scanty.

So, I think one can dismiss the diphenylmethane group as effective tranquilizers and just say they are available and you can use them or not.

Now we come to the substituted propanediols, which all of us know as Miltown and Equanil. They are mild sedatives. But we should remember that they, too, may be accompanied by toxic reactions.

One of the major selling points for meprobamate, as alleged proof of its superiority over the barbiturates, is that there is no habituation. I would be interested to hear what our psychiatric colleagues have to say about this. It seems to me that the literature is now replete with

cases of frank habituation, or withdrawal symptoms, especially in those persons who have been receiving the drug over long periods of time and have suddenly had it stopped. Physiologic and psychologic dependence on these agents does occur.

I also would like to mention the wide spectrum of side effects which may occur with the meprobamates. They are not harmless—gastric irritation, skin lesions, and others. So, before placing a patient on meprobamate, I would hesitate about giving it in preference to aspirin, the bromides, or to the short-acting barbiturates.

I have been asked to say a word about iproniazid (Marsilid). That word is "no". Dr. Malitz has given some of the pharmacology of this drug, as it applies to the treatment of psychiatric disturbances. Early in 1958 there appeared a report in the South American literature, of which many of you may have heard. An investigator in Mexico City reported that iproniazid was 100 per cent effective in the treatment of angina pectoris. Further, he postulated that its success in the treatment of angina was due to a specific effect of iproniazid on the heart. It is interesting to note that on the basis of, I believe, this single report, there appeared shortly afterwards an advertisement in *Lancet* suggesting that iproniazid be used in the treatment of angina pectoris.

This is the type of problem that one encounters all too frequently, and it is precisely the reason for being hypercritical of both isolated reports and drug advertisements. Shortly after this report appeared, I had an opportunity to evaluate the effect of iproniazid in cases of coronary artery disease. My own findings have been well corroborated by many clinicians, including Dr. Arthur Master of this city. Experience with this agent is that it certainly does not benefit 100 per cent of patients. I don't think any drug does that. However, it does seem to have a profound effect in relieving the pain in some 40 to 50 per cent of cases. At the same time, there is no objective evidence that iproniazid improves myocardial circulation. Whatever effect this drug does have, it is in the reduced perception of pain.

It may cause hypertension, which is a very bad thing in cardiacs, severe urinary retention and constipation. I have also seen a case of peptic ulcer associated with this drug. But, even if iproniazid were not so toxic as to militate against its use, one is presented with this problem: suppose a drug is finally found that does relieve angina, but does so without, at the same time, improving myocardial circulation. Are you

justified in removing the built-in danger signal which angina fortunately gives such patients? My answer to that is "No". I think that this same philosophical problem may pertain to many of the other tranquilizers.

In using these drugs one should be absolutely certain that they do not obscure any danger signals, or the many signs and symptoms of organic disease.

MODERATOR COTTON: I would like to emphasize a few things Dr. Rosenfeld has said, because I think they are very important in general practice. As you probably know, the number of older people now in our psychiatric hospitals, that are, in one way or another, becoming public charges, is increasing, and we have become acutely aware of the importance of using the chlorpromazines with these older people, particularly because of the danger of severe vascular collapse of depression. In the past two years in our New York State hospitals, where these drugs have been given, a number of deaths have been reported either with cerebral thrombosis or coronary thrombosis—many of these types of thrombosis seem directly related to the dosages of chlorpromazine. One is greatly tempted to give these drugs to elderly patients; and I must emphasize that in many cases they can be very helpful in making their lives more comfortable. In our hospital we require that all patients over 60 years of age who are given, for whatever reason, even small doses of chlorpromazine, must have their pulse, blood pressure and general circulatory status checked at least every four hours, until the dosage has been stabilized. This is the only way they can be protected against adverse effects.

Dr. Rosenfeld has raised a somewhat philosophical question, but I think it is an important one: if these drugs do what the advertising literature says they will—of course they don't really, but occasionally you do see some evidences of effective action—and even if it were possible, by judicious use of these drugs, to eliminate all reactive anxiety, are we justified in using them? Actually, isn't this anxiety somewhat analogous to the pain of angina pectoris, an important part of man's total condition and experience, his place in our society and perhaps a warning signal for him to slow down?

There is a very thoughtful and, I think, a very good statement* issued by the Committee on Public Health of this Academy, on the

* Report on tranquilizing drugs. Committee on Public Health, The New York Academy of Medicine. *Bull. N. Y. Acad. Med. 33:* 282-9, 1957. Reprints available on request to: Dr. H. D. Kruse, Executive Secretary.

whole subject of the use of these drugs.

We have a few questions which have been submitted by members of the audience directed to you, Dr. Malitz. We should be pleased to have the comments of the other panelists also. The first question says: *Would you please comment on the incidence of serious side effects, such as jaundice, with the various phenothiazines*—I suppose it means using brand names—that is, *which are the safest in this regard?*

DR. SIDNEY MALITZ: So far there seems to be greater safety in the drugs that have been introduced most recently. That may mean—and this again emphasizes the necessity of long-term observation—that they haven't been used long enough. Some of the newer phenothiazines, such as Trilafon and Compazine, are not particularly associated with jaundice. At the present time there seem to be fewer serious side effects with some of these newer drugs which are in the phenothiazine group. Actually, it is one of the goals of research in this area to determine whether, by slightly changing certain side-chains, the undesirable side-effects can be altered, modified and minimized, without reducing the desired clinical effects. All in all, Thorazine still appears to be the drug of choice; but it is also associated with the greatest number of side effects. Most of them are inconsequential, merely annoying and, fortunately, quite rare. The Parkinsonian picture, as are many cases of jaundice, is reversible, but in both instances these effects can also be quite distressing when they develop.

It does appear as if some of the newer drugs may have fewer of these side effects. However, with regard to Parkinsonism, interestingly enough it seems that those drugs which require milligram more, milligram less, also tend to produce the Parkinsonian picture earlier and more rapidly.

But again, there is tremendous variability. There is no rule of thumb. The drug dosage must be adjusted to each individual patient. When one drug proves ineffective, another should be tried to see whether it is effective and whether the side effects persist or disappear.

MODERATOR COTTON: I might add that those of you who have never met the severe Parkinsonian-like side effect that can occur, even with quite small dosage of any of the phenothiazines, will be startled to see how severe this effect can be. I have been awakened at least twice in the middle of the night by a physician who has seen his first case of this type and who was greatly disturbed because of the intense dystonia.

The contortions almost resemble those of convulsions. Although conscious, the patients writhe in a strange way. It is quite frightening. With use of mild sedatives, just a little patience, and time, the episode subsides, and there do not seem to be any serious sequelae in such cases.

DR. MALITZ: I might add to Dr. Cotton's remarks that there are two types of Parkinsonian picture. The first, which is easy to recognize, is post-encephalitic. Some of the most acute cases do resemble hysterical reactions or fits. The patient may have a peculiar spasm of arms and legs which looks like hysterical reaction. These things can be quite frightening.

I think it is also important to mention that with these drugs we occasionally see another effect, the so-called Herxheimer reaction, which is a condition marked by greatly increased restlessness and motor activity; the patient can't sit and he can't stand, and this may be mistaken for greater anxiety. In this situation the patient may be given more of the drug and may thus become worse. In those instances the dosage of the drug should be reduced or stopped altogether.

These reactions seem to occur more commonly with the newer phenothiazines, Compazine and Trilafon, which are used in smaller dosages than were employed with the original prototype, thiazine.

DR. ISADORE ROSENFELD: There was a review by Dr. Lehman of McGill in the *Canadian Medical Journal*, in which he summarized the incidence of these effects. He concluded that the incidence of cholangitic hepatitis jaundice is about one per cent. The first report indicated it was four per cent; now it is one per cent. The incidence of agranulocytosis was approximately one to five in ten thousand. The incidence of Parkinsonism was between 10 and 50 per cent of cases receiving large doses of the drug over a long period of time.

MODERATOR COTTON: Some of these products have been introduced with claims that they do not produce jaundice or Parkinsonism. By the time they have been in use for six months, you will find such claims slowly being withdrawn from the advertising literature.

I think that, by and large, they have very much the same side effects if they are derived from the same basic chemical compound. The fact that they produce these intense reactions should indicate to all of us that we are dealing with powerful drugs. We don't know what they are doing, or how they are doing it. We should be cautious.

I have a question for you, Dr. Rosenfeld, a question regarding a

specific type of case. *If you have a case with ventricular paroxysmal tachycardia, and the use of quinidine produces diarrhea, what substitute drug would you use, other than digitalis?*

DR. ROSENFELD: I would use procainamide. That is the drug that comes to mind immediately. I would not use Atarax. Also, unless there is gross congestive failure, digitalis is definitely contraindicated. I wouldn't use any of the "benign" agents. There have been reports recently in the literature concerning the use of two agents; one is intravenous Dilantin. I have no personal experience with the use of this drug in this particular situation. The other report refers to the use of one of the chelating agents, Edta, which is a calcium binder. I have had no personal experience with the use of this drug either. Whoever asked the question may wish to refer to the literature on these two agents.

DR. MALITZ: Present day central nervous system stimulants are divided into two main groups: amphetamines and non-amphetamines. Amphetamines have been used for many years and include such old stand-bys as Benzedrine and Dexedrine. Non-amphetamine stimulants are a relatively recent innovation and include drugs such as Meratran and Ritalin. While claims have been made that the latter group are superior to the amphetamines because they are associated with much less side effect, it has been my experience that restlessness and interference with appetite and sleep can and does occur with both groups, although there may be individual differences, of course, among patients. It is sometimes wise, therefore, to switch from one group to another, if side effects prove troublesome, since the possibility exists that they will be less with another group.

As far as effectiveness against depression, these drugs still leave much to be desired. While of benefit in mild depressions, they are relatively ineffective in severe depressions. In the latter, electric shock still appears to be the treatment of choice.

MODERATOR COTTON: It is extremely difficult, as most of you know, to evaluate these drugs in psychiatric patients. There have been any number of studies concerned with evaluation. It has been suggested by one careful investigator that no drug should be considered as having any effects whatever, until it shows a good effect in more than 33 and a third per cent. If a pure placebo is given to a group of psychoneurotic patients, you can confidently expect to find that at least one third of them are helped, one third get no effect, and a third are made worse.

This has been found repeatedly. So, when any newly introduced drug is given to psyschoneurotic patients, it is often extremely difficult to evaluate both the primary and side effects.

In an ambulatory, employed patient who has an agitated neurosis, and a tranquilizer is indicated, is there any contraindication to combining it with Marsilid, to combat the drowsiness that the tranquilizer may cause?

DR. MALITZ: On general principles, I would not combine it with Marsilid, about whose toxicity you have heard. I think it is difficult enough to observe and evaluate the effects of the Marsilid alone, without complicating the picture by giving it with another drug. I would, however, combine some of the phenothiazines or reserpine, with one of the amphetamines or even Ritalin, and this is sometimes helpful in off-setting the drowsiness that you mention.

Interestingly enough, even drowsiness has a factor associated with it that may be subjective, and tends to depend on the environment in which a patient is located. For example, using the same drug that we used on out-patients, we found that on in-patients we could increase the dosage up to five times greater; out-patients would complain on similar dosages. Many of them were going to work, and they were more aware of such symptoms as drowsiness and mechanical ineptitude, whereas the in-patients, not being put under the stress of work, could take much higher dosages of the same drug without complaining.

CHAIRMAN COTTON: In connection with the question of dosage of Thorazine when used by the general practitioner, it is difficult to give any rule. Occasionally, in very disturbed and seriously psychotic people, we give doses as high as three or four thousand mg. a day, without too much difficulty. In ordinary practice with ambulatory patients, I don't think that doses of more than 200 mg. a day would ever be justified. I think doses larger than this should be given only in a hospital, or by someone who has had a wide experience with this drug. Would you agree with that?

DR. MALITZ: I certainly would.

MODERATOR COTTON: I wish to thank the members of the panel for their presentations and discussion and the audience for its sustained attention.

ANTIBIOTICS—20 YEARS LATER*

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THE causes of the majority of diseases that afflict man, his herds, and his crops, were still unknown as late as a century ago. There were at that time only very few, among both the scientists and the medical practitioners, who surmised the contagious nature of infectious diseases. It is true that numerous theories were afloat, postulating the existence of living contagious agents, but exact proof was lacking. About 1860 the great physiologist, Claude Bernard, wrote that "the present state of medical practice suggests that a solution [to the problem of conserving health and of curing disease] is still far to seek." Little did Bernard dream that both the understanding of the causes of most infectious diseases and methods for combatting them were soon to follow. His own protégé, Louis Pasteur, was to become the leader in the new concept of microbes, both as causative agents and as possible means for treating infections. Prophylaxis by means of vaccination and serotherapy was soon to be followed by true chemotherapy. It is the latter, or rather one phase of it, with which I am concerned here.

Just a little over 40 years ago, or towards the end of and soon after World War I, I was personally concerned, on the one hand, with the problem of manufacturing Salvarsan, the first true chemotherapeutic agent that found extensive application in the treatment of one of the most serious infectious diseases, and, on the other, with the study of the microbiological population of the soil, particularly involving a little-known group of microorganisms, the actinomycetes. I thus came to visualize, early in my scientific career, the great potentialities of chemotherapy in the treatment of infectious diseases. As I watched the unfolding of the great biochemical potentialities of the actinomycetes, I little dreamed that the time would come when the two so apparently distinct phases of my career would in time be joined together to yield some of the greatest tools for combatting infectious diseases placed at the disposal of man, the antibiotics.

* Presented at the meeting of the Section on Historical and Cultural Medicine, The New York Academy of Medicine, May 25, 1960.

Twenty years have passed following these first observations. The world was now approaching another World War. In the meantime, the sulfonamides had been discovered. Here were new and better drugs. But still they were not, at that time at least, the most ideal agents for combatting numerous bacterial and other infections, many of which were not even sensitive to them. The study of the biochemical activities of the actinomycetes had made only little progress during that period. It is true that definite evidence was being submitted to the fact that these organisms possess powerful mechanisms for inhibiting the growth of various bacteria and fungi. The possible utilization of such mechanisms in the control of infections was gradually becoming recognized.

The years 1939-1940 were momentous ones in the history of antibiotics. Three important discoveries brought to a head the gradually accumulating information concerning the great potentialities of several groups of microorganisms to produce chemical substances that have the capacity to inhibit the growth of different disease-producing bacteria and fungi. These substances were shown to be active not only in the test tube, but also in experimental animals. A group of aerobic spore-forming bacteria was found by Dubos capable of producing antimicrobial substances, designated as tyrothricin. The capacities of certain fungi to form antimicrobial agents was reemphasized through the rediscovery of penicillin by Florey and Chain. The abilities of actinomycetes as producers of powerful antibacterial and antifungal agents resulted in the isolation of actinomycin in crystalline form in our own laboratories. Of these three types of compounds, penicillin soon began to make history. Tyrothricin remained what came to be known as a "minor" antibiotic. Actinomycin was found to be too toxic for therapeutic use; however, the ease of its formation and isolation encouraged us to search for other antimicrobial substances produced by the same group of organisms, namely the actinomycetes, leading finally to the isolation of streptomycin in 1943.

The following five years witnessed the laying of the groundwork for this new branch of science, resulting in tremendous developments in medical and veterinary science, in animal nutrition, and in the preservation of food and other biological materials. The very name "antibiotic" was introduced at that time. Penicillin was now manufactured on a large scale; greater yields and new forms were being obtained. The actinomycetes were yielding one new antibiotic after

another. Whereas tyrothricin and penicillin were active largely upon diseases caused by cocci and gram-positive bacteria, streptomycin was also active upon diseases caused by various gram-negative bacteria causing tularemia, undulant fever, typhoid, dysentery, plague, cholera, and a variety of other infections. Most important of all, however, was its ability to act upon the tuberculosis organism.

It is now exactly 15 years since the effectiveness of streptomycin in the treatment of tuberculosis was established. This powerful drug proved to be highly effective against the ancient enemy of man, the Great White Plague, to which a death blow was thus delivered. Although streptomycin had its limitations, it pointed the way, thus leading later to the isolation of other antibiotics and synthetic compounds that would tend to overcome them. Who could ever dream that less than a decade and a half later, the following statement would be made:

> "The balance between the tubercle bacillus and man has finally given way in favor of man. The decline in the number of infections and in the number of active cases and deaths is a very real indication of this change in balance. The continuity of this trend and its extent, increasing as it has in recent years, justify the conclusion that the balance has already been so far disturbed as to give the highest hope for complete control of the disease. . . . We cannot say exactly when control will be complete, but there is every indication that it will be some time in the course of the next 20 years" (L. Dublin).

The same idea was further emphasized in a recent issue of the WHO *Chronicle* (November, 1959):

> "The new situation created by the advent of potent antituberculous drugs —first streptomycin in 1944, then PAS and isoniazid—has come upon the world almost unawares, and the profound implications it carries are only just beginning to be grasped. For millions of people throughout the world there is now hope of recovery, whereas previously there was none. The medical profession too is now faced with a change in methods of treatment and prevention of tuberculosis that may alter its approach to problems of control."

But to continue my story. Just as penicillin in 1941-1944 was not the last word in the treatment of staphylococcal and other infections caused by gram-positive bacteria, so streptomycin in 1944-1946 was not the last word in the treatment of tuberculosis and of infections caused by gram-negative bacteria. The next decade was to witness the advent of a large number of other antibiotics and of synthetic compounds, to supplement the other two. Chloramphenicol and the tetracyclines were soon isolated, and came to be dubbed in certain quarters as the "broad spectrum" antibiotics, because of their activity upon the intracellular

parasites, namely the rickettsial organisms and the members of the psittacosis-lymphogranuloma group, in addition to their effect upon various gram-positive and gram-negative bacteria.

The extensive use of antibiotics, that soon came to be known in the popular mind as "miracle drugs," began to bring many problems with them. Certain severe reactions, due either to sensitization or to particular idiosyncrasies of some individuals, were to be expected. Much more general and therefore more important was the development of resistance to the older and more extensively used antibiotics, notably penicillin and streptomycin. To meet these limitations two approaches were now developed, one consisting in the combination of these with other antibiotics or with synthetic compounds, and the other comprising the isolation of new antibiotics to which the resistant organisms were sensitive. Thus came into practical use, under a variety of different names, combinations of penicillin with streptomycin, of streptomycin with dihydrostreptomycin or with PAS and INH, and a variety of others. Numerous new antibiotics were isolated. An attempt to overcome the growing resistance of the tuberculosis organism to streptomycin led to the isolation of neomycin, viomycin, cycloserine, and others. Penicillin resistance led to the isolation of erythromycin, novobiocin, oleandomycin, vancomycin, and many others.

Other groups of disease-producing microbes not sensitive or insufficiently sensitive to the first antibiotics were not overlooked. Bacitracin, a bacterial product, was found to be primarily active against gram-positive bacteria; polymyxin, also a bacterial product, was active largely against gram-negative bacteria; nystatin, an actinomycete product, and griseofulvin, a fungal product, were both active upon disease-producing fungi; a variety of other antibiotics active upon bacteria, fungi, and protozoa soon came into the field to occupy important places in human and animal therapy. The effect of antibiotics upon various plant diseases was studied and effective results obtained, as illustrated by the use of cycloheximide and streptomycin. Animal feeding and food preservation came to be benefited from the use of bacitracin, the tetracyclines and some of the older antibiotics, notably penicillin and streptomycin.

Within fifteen years after the successful introduction of the first three effective antibiotics, some 30 compounds came into practical use as important chemotherapeutic agents. A new field of science and applica-

tion was opened up. Diseases that only a generation ago were thought to be incurable became subject to successful therapy. This was true of the various diseases of childhood, as well as of pneumonia, dysentery, typhoid and typhus fevers, plague and cholera, tuberculosis, and of a variety of other infectious diseases, caused by bacteria, fungi, and protozoa.

Unfortunately, this cannot be said of diseases due to virus infections and of various organic diseases, the exact etiology of which, in many instances, still remains unknown. Although some definite progress appears to have been established in the treatment of some of these diseases, notably in cancer, the tremendous efforts made in this direction have so far not been sufficiently justified. We can hardly speak of any agent that would be active upon diseases caused by viruses, although a number of preparations that were at first believed to be effective have been isolated and described under different names. This is true, for example, of ehrlichin, xerosin, abikoviromycin, violarin, and others. A number of different antibiotics have been recorded as capable of exerting certain definite, if not always favorable, effects upon neoplasms. This is true of azaserine and DON, of sarkomycin and carzinophilin, of puromycin and mitomycin, and finally, of actinomycin.

Let me cite the last one for further illustration. As I said previously, actinomycin was the first antibiotic that was isolated in our laboratories in 1940. Although it was easily obtained in pure crystalline form and although its peculiar effects in reducing the size of the spleen were demonstrated soon after its isolation, only little attention was paid to this observation, since we were interested at that time only in its antibacterial properties. As an antimicrobial agent, it proved to be useless for therapeutic use, because it was too toxic. Several forms of it were isolated later in our own and in other laboratories throughout the world. As a matter of fact, any new screening program for antibiotic production by actinomycetes always yielded actinomycin as its first product. It is now known that a number of different species of *Streptomyces*, and as many as 10 or more per cent of all actinomycetes freshly isolated from the soil, are capable of producing this antibiotic. Various forms of it, differing in activity and toxicity, have been reported.

More than a decade passed, however, before Domagk and his group in Germany demonstrated that actinomycin has a marked effect upon certain neoplasms. According to these investigators, one form of actino-

mycin, designated as C, was able to repress the development of Hodgkin's disease. These observations attracted universal attention, including our own. We soon succeeded in isolating a new type which we designated as actinomycin D, and in demonstrating its efficacy in suppressing various experimental tumors. Much evidence soon began to accumulate, as illustrated by a symposium held March 31- April 1, 1960 at the New York Academy of Sciences. The study of the actinomycins entered a new phase. Numerous new compounds have now been isolated, either by using different organisms capable of producing them or by modifying the composition of the medium through the addition of various amino acids, such as sarcosine, proline, valine, etc. The different compounds show not only quantitative, but also qualitative differences in antitumor properties.

The field of antibiotics has now reached many ramifications. To attempt to summarize all of these would take us too far afield. It is sufficient to examine here some of them, even if only in broad outline.

Chemical Structure vs. Biological Activity

The following questions pertaining to the antimicrobial activities of antibiotics logically present themselves:

Why do some antibiotics act upon bacteria alone, others on fungi alone, and still others upon both bacteria and fungi?

Why do some affect rickettsiae and the psittacosis-lymphogranuloma group of intracellular parasites, but not the smaller viruses?

Why are the gram-positive bacteria far more sensitive to the great majority of antibiotics produced by actinomycetes and other microorganisms than are the gram-negative bacteria?

Why do some antibiotics have a marked activity upon acid-fast bacteria and not others, even those that are active upon various gram-positive organisms?

Why do some bacteria and not others develop rapid resistance to some of the antibiotics, as is the case of staphylococci *vs.* streptococci to penicillin?

Why do the rates of development of resistance differ for different antibiotics, as in the mechanism of development of resistance among sensitive bacteria to penicillin *vs.* streptomycin?

Why do some bacteria produce strains that become nutritionally dependent upon certain antibiotics, as in the case of streptomycin?

Were answers found to the above questions, one could go a long way in establishing the correlation between chemical structure and biological activity of the various antibiotics.

Even if these questions cannot be answered as yet at the present time, advantage is taken of some of the unknown properties of the antibiotics in classifying them, utilizing them, and suggesting an interpretation of their possible mode of action. The phenomenon of resistance and sensitivity of microorganisms to various antibiotics permits at least the recognition of certain close relationships among such antibiotics, if not in their chemical structure, at least in their biological activity. Thus the similarity among antibiotic preparations may be recognized long before their chemical nature has been established. Although it is now fully recognized that the mode of action of various antibiotics upon sensitive bacteria and fungi differs, too little is known about this phase of antibiotic behavior to make possible speculation upon any relationships that may exist between structure and activity.

The toxicity of antibiotics to animal tissues is known to differ greatly. This phenomenon is of great importance in any attempt to evaluate the practical potentialities of antibiotics in disease control. The actual reasons for this are largely obscure. Neomycin, for example, was shown to be an excellent agent in the treatment of tuberculosis, but so far it has not found any important place in the armamentarium of phthisiologists, largely because of its injurious nephrotoxic and ototoxic effects when administered parenterally. Different modes of administration or the supplementation of certain nutritional factors, like pantothenic acid or glucuronic acid, have been found to be the answers for the practical utilization of this antibiotic orally or topically, but so far not parenterally.

Although it has been assumed that the *in vivo* activities of the antibiotics are parallel to their *in vitro* action, there are certain instances when such parallelism is not evident. This is true, for example, of cycloserine, an antibiotic said to be more active against the tubercule bacillus *in vivo* than *in vitro*, although more recent evidence seems to suggest that this is not the case.

Attention must also be called to the fact that actinomycetes produce various growth-promoting substances, notably vitamin B_{12}, and that some antibiotics, in limited concentrations, may also exert a growth-promoting effect upon various forms of life; this property has been

taken advantage of in the nutrition of poultry, swine and other animals. These phenomena tend to complicate further our concept of the chemical structure and biological activity of antibiotics.

In order to emphasize that certain changes in the chemical structure of the antibiotic molecule may result in marked changes in its biological activity, the following illustrations will suffice:

1. When streptomycin is changed chemically to dihydrostreptomycin, whereby the carbonyl group in the central hexose unit is reduced, the characteristic antibacterial properties of the drug are retained, although there is a change in the nature of its potential toxicity. On the other hand, the treatment of streptomycin by such carbonyl reagents as hydroxylamine brings about its inactivation. The replacement of the CH_3 group in the central hexose unit (streptose) by CH_2OH, to give hydroxystreptomycin, seems to increase its toxicity without apparently interfering with its activity.

2. The modification of the aromatic aryl, the dichloroacetyl, and the CH_2OH groups in the chloramphenicol molecule results in the complete destruction of its activity.

3. The degradation of chlortetracycline to tetracycline, whereby the chlorine atom in the first ring is replaced by a hydrogen atom, results only in certain minor changes in the antimicrobial activities of the molecule, and is believed to give a less toxic compound.

4. The activity of actithiazic acid against the tuberculosis organism has been related to its thiazolidone structure.

These facts are too limited to justify any broad generalization concerning specific structure and activity of antibiotics. One point is clear, however, that the antibiotics of actinomycetes represent such a wide variety of chemical structures and of biological activities that one cannot help but conclude that we are dealing here with a new field of natural products, varying greatly in chemical composition, in antimicrobial activities, and in other biological properties that render them of great importance in human health and in human economy.

Contributions of Antibiotics to Fundamental Science

Aside from their importance in the treatment of infectious diseases in man, animals and plants, antibiotics have contributed materially to various fields of science. In the hands of qualified investigators, the antibiotics have become powerful tools for further scientific research.

This is true particularly of the fields of chemistry and biology, especially in their application to agriculture, medicine, and public health. A few illustrations will suffice:

1. The knowledge of antibiotics has contributed greatly to genetics, especially microbial genetics. The development of bacterial resistance to streptomycin and to other antibiotics proved to be a very important genetic marker for studies on the sexual recombinations both among bacteria and actinomycetes. Crossings of parental strains with rearrangement of genetic materials are usually performed with nutritionally deficient mutants of strains that normally can grow in synthetic media with a sugar as the sole carbon source. Penicillin is usually employed to concentrate and recover the induced mutants.

2. A better understanding of biological synthesis, especially of large molecules, notably proteins, nucleic acids, and cell wall material has been greatly facilitated by the introduction of antibiotics. The effect of chloramphenicol on the building of the protein molecule and the amino acid incorporation established the fact that this antibiotic uncouples the synthesis of nucleic acid from that of protein. This is also true of the effect of penicillin upon protoplast formation in *Escherichia coli.*

3. The widespread use of antibiotics has stimulated organic chemical research, and several new or very rare compounds have thus been discovered. Streptose, the first branched chain sugar to be identified in a microbiological product, was found in streptomycin; this is also true of streptidine, a base related to inositol. Only three naturally occurring polyacetylenes were known before 1950, but the study of the polyene antibiotics has increased the number to at least 25. Dichloroacetic acid and nitrobenzene, though known to the organic chemist, were found in a natural product for the first time in chloramphenicol.

4. The very fact that there is relatively little cross-resistance among the various antibiotics suggests the probability that different mechanisms of antimicrobial activity are involved. This effect of antibiotics upon microbes causing infectious diseases offers the clinician a number of possibilities in the selection of chemotherapeutic agents, alone or in combination with other antibiotics or chemical substances. The whole principle involved in the preparation of polio vaccine is based on the preservation of the polio viruses against destruction through bacterial contamination, by means of antibiotics.

5. The growth-promoting effects of antibiotics on higher animals

appear to be distinctly different from those exerted by essential growth factors or vitamins. It is not so specific as is the case for true vitamins. It involves processes heretofore scarcely recognized in nature. This stimulating effect of antibiotics has been ascribed to a disturbance of the intestinal microbial populations of the animals. A direct effect upon animal growth has also been postulated. Since antibiotics may affect adversely the bacterial population of the rumen, which assists the animal in the digestion of its cellulosic food materials, care is needed in the use of antibiotics only at a certain stage of development of the animal.

6. Human and animal semen can be preserved from bacterial attack by means of antibiotics. The same is true of the preservation of foods, especially poultry and certain vegetables. Since antibiotics do not inhibit all forms of microbial life, more than one antibiotic may, therefore, be required for proper preservation. Before the food is eaten, however, the antibiotics must be destroyed by boiling, for their constant consumption in food would tend to have certain dangerous effects upon the human body.

7. Antibiotics have introduced a new concept in our understanding of microbial life in natural environments. They have added greatly to our understanding of various aspects of biology, under natural conditions. The actinomycetes have proved to be the richest source of antibiotic producers. In 1939, on the eve of the advent of antibiotics, these organisms were considered as a rather insignificant group of microbes, largely inhabiting soils, composts, and lakes. Today, because of their ability to form antibiotics, as well as certain enzymes and vitamins, their biochemical activities and their role in nature have become problems of paramount significance.

8. Numerous other solutions of scientific problems have been made possible through the discovery of the potentialities of antibiotics. These include the extensive use of tissue cultures in biology, a better understanding of the structure of the bacterial cell, studies of superinfections, and other problems in the field of medical research.

Utilization of Antibiotics

The antibiotics have come to occupy a prominent place, together with enzymes, hormones, and vitamins, among the products of living systems that influence the growth of both higher and lower forms of life. They have become, in a way, the control mechanisms of life and

of living processes. By learning to utilize antibiotics, man has greatly simplified the problem of his survival on earth.

The potentialities of the practical utilization of antibiotics in the life of modern man are still far from exhausted. Wherever man has had to face microbes, be they injurious to his own health or to that of his herds and crops, be they destructive to his industrial products or to his foodstuffs, he has found and will continue to find in the antibiotics powerful weapons of combat.

However, as with other great discoveries that have revolutionized human life, new problems have arisen as a result of the introduction of the antibiotics. Among these are the social and economic problems that have resulted from an increase of nearly twenty years in the average life span of man. New public health problems have arisen from the practical control of many infectious diseases, notably those of childhood, of the respiratory system, of the gastrointestinal, the circulatory systems and of tuberculosis. The disturbance in the natural microbiological equilibrium by the extensive use of chemical agents that tend to eliminate certain members of the microbial population and not others, may not only stimulate the development of resistant strains but also lead to the appearance of potential undesirable mutants of microbes. The reduced natural resistance in the human and animal body as a result of the elimination of the infectious organisms also has dangerous potentialities. Some of these implications deserve particular consideration.

What Does the Future Hold?

It is believed in some quarters that the development of resistance to antibiotics suggests their reduced usefulness and gradual elimination. As new antibiotics are introduced, these, as well, are later followed by the development of resistance to them. The gloomy prophet tends to see in this the end of the antibiotic era. The optimist, however, is greatly heartened by the progress already made. He foresees in the near future the complete elimination of tuberculosis as the great enemy of man; he looks forward to the complete control of children's diseases. Such infections as undulant fever, typhoid, dysentery, cholera, plague, and venereal diseases no longer hold for him the threat that he has faced prior to the advent of the antibiotics. He even looks forward to the potential attack upon such diseases as those caused by viruses and cancer. How soon this may come about, only the future can tell.

PRINCIPLES OF FREE SKIN GRAFTING*

JOHN DAVIES REESE** and RICHARD BOIES STARK†

HISTORICALLY, full-thickness grafts of skin were first transplanted successfully in the sheep by Baronio of Milano in 1804; and in the human by Buenger of Germany, in 1823, and by Jonathon Mason Warren of Boston, in 1840.

Small pinch-grafts were popularized by Reverdin in 1869, as were sheets of partial-thickness skin by Ollier in 1872 and Thiersch in 1886.

Grafts of skin may be classified in several ways but basically are divided into four categories:

1. Epidermic
2. Dermic
3. Partial-thickness (thick-split)
4. Full-thickness

Practically speaking, partial and full thickness grafts represent approximately 90 per cent of all grafts currently used.

Free grafts of skin are hardy indeed, and if certain prerequisites are met, may be transplanted successfully in many ectopic sites; as for example, lining for or replacement of the orbital, nasal, oral and middle ear cavities; to provide a tympanic membrane; to reconstruct the common bile duct, aorta, urethra, or ureter; to surface a part of the stomach and peritoneal cavity; to line the bladder; to form a vagina; and to aid in the reconstruction of the hip joint.

How a Free Graft of Skin Grows

When viewed macroscopically, the initial appearance of a free graft of skin is milk-white and edematous; and there is good reason for this. During the first 72 hours, the transplant survives by plasmatic diffusion of nutrients and metabolites. The strong negative charge

* Presented by Dr. Stark at the Meeting of the Section on Otolaryngology, The New York Academy of Medicine, November 16, 1960.

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(pH 4 or less) of the mucopolysaccharides and mucoproteins of the ground substance permits the ready diffusion of cations, for, in the first 72 hours, the graft survives not by circulation of blood but by gradients in hydrostatic and osmotic pressures between capillaries and venules, tissue spaces, and lymphatics that produce a "plasmatic circulation" by means of which most cells of the body are nourished and which has been described well by the late John D. Reese.

The "plasmatic circulation" works in this fashion: Hydrostatic pressure at the capillary end of the capillaryvenule "glomerulus" of the skin is slight, yet it is sufficient to drive crystalloids through the interendothelial cement substance into the tissues, where they become "tissue fluid". Once it has filtered through the capillary walls, tissue fluid flows easily between fibers of collagen and elastin, imbedded in mucopolysaccharides of the ground substance.

To circulate, however, tissue fluid must be absorbed; it is absorbed in two ways. First, it may be absorbed by lymphatics, endothelial tubes that end blindly in the rete pegs of the dermis. Lymphatics open because connective tissue fibers are attached to the endothelium from without, pulling open the ends of the lymphatics so that, as tissue fluid accumulates in the extra-cellular spaces, it exerts pressure upon these connective tissue spring latches and forces open the lymphatics more widely. A pressure gradient exists between tissue fluid outside and within the lymphatics, which roughly is from 1.5:1 to 6:1, producing absorption. Once tissue fluid enters the lymphatics, it is referred to as lymph. Lymphatic capillaries drain into larger vessels, thence into main trunks by means of which lymph returns to the hemic circulation.

Second, tissue fluid may return more directly to the blood circulatory system by absorption. Since blood contains more colloid (8 per cent protein) than tissue fluid (2 per cent protein), this gradient is sufficient to attract fluid from the extra-cellular compartment into the venous end of the capillary-venule "glomerulus". The hydrostatic pressure that produced filtration *initially* has fallen, so that it cannot overcome the attraction of the osmotic pull.

When an open wound exists, however, plasmatic circulation ceases, since tissue fluid escapes through the portal of the wound and is not absorbed by either lymphatics or venules. A free graft of skin serves, therefore, a most important function, acting as a seal to restore vascular and tissue fluid balance so that the dynamics of plasmatic and hemic

circulation may recommence. The analogy to transplanting, therefore, is less apt than to sealing, and in this instance to sealing a leaky faucet; hence, one who engages in the grafting of skin is probably less comparable to a horticulturalist than to a plumber (Reese).

But support of a skin transplant by plasmatic circulation is short-lived, since vascular anastamoses from the bed of the host occur as early as 48 to 72 hours following transplantation (Edgerton). During this period, erythrocytes move sluggishly into the arteriole-capillary-venule network of the graft, where, macroscopically, their unoxygenated condition imparts a bluish mottling to the graft surface.

The hemic circulation about the periphery of a graft is achieved by peripheral capillary buds which grow towards the graft by seemingly purposeful orientation (Conway and Stark). Arborization of the new vessels occurs, producing many parallel branches which all grow towards the graft. It is not certain whether this is due to a chemotactic stimulus or to a network of reticulum within the bed of the host. The flow of blood may be detected microscopically in new capillary buds as early as the fourth day, when cells exhibit a to-and-fro movement. As soon as anastamoses of new capillaries with those of the graft are achieved, however, hemodynamics dictates the direction of blood flow in the capillaries. At this point, the bluish mottling changes to a pink coloration.

Once the transplant has obtained its vascular purchase upon the bed of the host, peripheral cellular union of graft to host occurs due to epithelialization from transplant and host; i.e., a sort of tidying up. Howes has shown epithelial growth to occur at the rate of 0.5 millimeters per day.

Prerequisites for the Survival of a Free Graft of Skin

GRAFT: 1. It is axiomatic clinically that the thinner the graft, the greater is the likelihood of successful transplantation. This is true, since epidermis normally survives by plasmatic circulation, which is the mode of survival of all free grafts of skin for the first two to three days, as has been discussed.

2. A graft must be completly immobile following transplantation, for the subtle plasmatic and fragile capillary circulations will function only if the graft does not shift upon its bed, a happenstance that will produce lymphatic and capillary rhexis.

3. The graft must adhere intimately to the bed. The interposition of any substance between graft and bed of the host (hematoma or seroma) will result in partial or complete loss of the transplant. The thromboplastin of the cut surface of the graft will aid hemostasis and should be preserved.

HOST BED: 1. The bed of the host must be sufficiently vascular to support a free graft of skin. Of the recipient tissues which may be called upon to provide a bed for a graft, dermis and cancellous bone are best, whereas fat and cartilage and cortical bone devoid of perichondrium or periosteum are poor.

2. A bed contaminated or infected by organisms (such as *beta hemolytic streptococci* or *pseudomonas aeruginosa*) will either destroy the graft or produce sufficiently liquid exudate to float the graft away from the bed.

In conclusion, the fate of a free graft of skin is decided by the time that its circulation switches from plasmatic to hemic, or at about the fourth day following transplantation.

The prerequisites of successful free skin graft are a graft devoid of fat kept immobile and in intimate approximation to its bed, which must be vascular and uninfected. Given this set of favorable circumstances, one should be able to transplant successfully grafts of skin.

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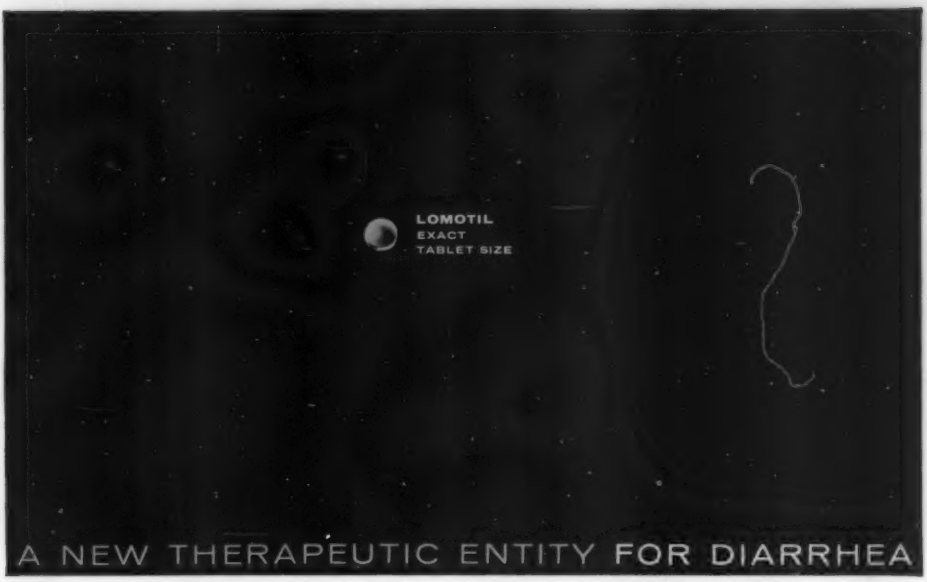

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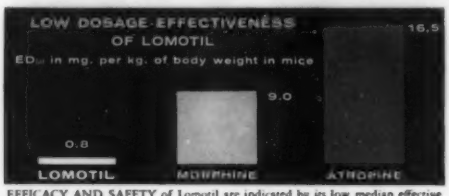

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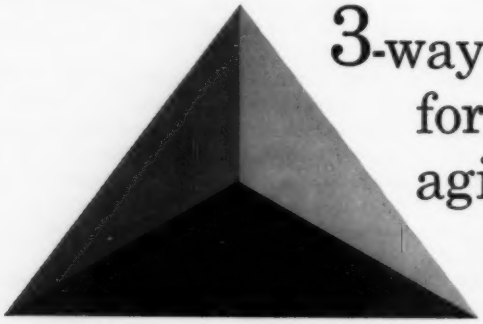

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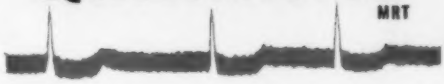

because QUINIDATE provides a full .2 Gm. (3 gr.) of quinidine sulfate in each 1 ml. ampul — added convenience for the physician, added comfort for the patient.

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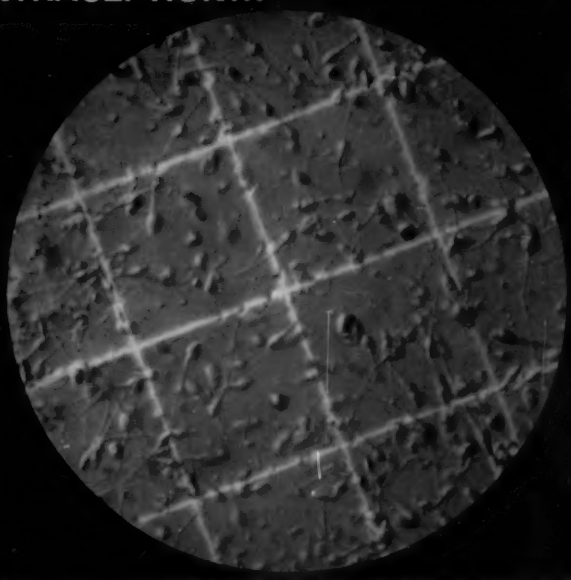

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Because the active ingredients of a spermicidal preparation must diffuse rapidly into the seminal clot and throughout the vaginal canal to be clinically effective. Lanesta Gel offers this *dual* protection. Its four spermicidal agents quickly invade the clot to stop the main body of sperm. It spreads evenly and quickly throughout the vaginal canal—seeks out every wrinkle and fold that may offer concealment to sperm. With this rapid diffusion, your patient receives full benefit of the swift spermicidal action of Lanesta Gel — in minutes — a decisive measure in conception control.

In Lanesta Gel *7-chloro-4-indanol,* a new, effective, nonirritating, nonallergenic spermicide, produces immediate immobilization of spermatozoa in dilution of up to 1:4,000. The addition of 10 per cent NaCl in ionic form greatly accelerates spermicidal action. Ricinoleic acid facilitates rapid inactivation and immobilization of spermatozoa and sodium lauryl sulfate acts as a dispersing agent and spermicidal detergent.

Lanesta Gel with a diaphragm provides one of the most effective means of conception control. However, whether used with or without a diaphragm, the patient and you, doctor, can be certain that Lanesta Gel provides faster spermicidal action — plus essential diffusion and retention of the spermicidal agents in a position where they can act upon the spermatozoa.

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Supplied: Lanesta Exquiset® . . . with diaphragm of prescribed size and type; universal introducer; Lanesta Gel, 3 oz. tube, with easy clean applicator, in an attractive purse. Lanesta Gel, 3 oz. tube with applicator; 3 oz. refill tube — available at all pharmacies.

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NERVOUS SYSTEM

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Seymour Soloman
Assistant Clinical Professor of Neurology
College of Physicians and Surgeons, Columbia University

CONVULSIVE DISORDERS

Sidney Carter
Professor of Clinical Neurology
College of Physicians and Surgeons, Columbia University

March 14, 1961

THE DEMYELINATING DISEASES

Marron Marks
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New York University School of Medicine

NEUROMUSCULAR DISEASES

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Assistant Professor of Neurology
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